Elevated dietary salt suppresses renin secretion but not thirst evoked by arterial hypotension in rats

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Elevated dietary salt suppresses renin secretion but not thirst evoked by arterial hypotension in rats. Am J Physiol Regul Integr Comp Physiol 284: R1521–R1528, 2003. First published March 6, 2003; 10.1152/ajpregu.00658.2002.—Increased dietary salt intake was used as a nonpharmacological tool to blunt hypotension-induced increases in plasma renin activity (PRA) in order to evaluate the contribution of the renin-angiotensin system (RAS) to hypotension-induced thirst. Rats were maintained on 8% NaCl (high) or 1% NaCl (standard) diet for at least 2 wk, and then arterial hypotension was produced by administration of the arteriolar vasodilator diazoxide. Despite marked reductions in PRA, rats maintained on the high-salt diet drank similar amounts of water, displayed similar latencies to drink, and had similar degrees of hypotension compared with rats maintained on the standard diet. Furthermore, blockade of ANG II production by an intravenous infusion of the angiotensin-converting enzyme inhibitor captopril attenuated the hypotension-induced water intake similarly in rats fed standard and high-salt diet. Additional experiments showed that increases in dietary salt did not alter thirst stimulated by the acetylcholine agonist carbachol administered into the lateral ventricle; however, increases in dietary salt did enhance thirst evoked by central ANG II. Collectively, the present findings suggest that hypotension-evoked thirst in rats fed a high-salt diet is dependent on the peripheral RAS despite marked reductions in PRA.

angiotensin II; water intake; blood pressure

An alternative approach to reduce the activity of the peripheral renin-angiotensin system (RAS) is to increase dietary salt intake, as basal levels of plasma renin activity (PRA) are inversely related to dietary Na⁺ intake (12), and elevated salt intake has been demonstrated to blunt stimulated increases in renin secretion (12, 15, 16, 28). An advantage of manipulating the activity of the peripheral RAS by altering the amount of dietary salt is that this approach does not rely on pharmacological or surgical procedures. If hypotension-induced thirst is due to increased activation of the peripheral RAS, and elevated salt intake blunts stimulated increases in renin secretion, then rats maintained on a high-salt diet should exhibit a smaller increase in renin secretion and therefore ingest less water in response to decreased AP. To test this hypothesis, rats were maintained on 1% (standard) or 8% (high) NaCl diet for at least 2 wk, and water intakes were measured after administration of DZX. Initial studies indicated that increased dietary salt did suppress renin secretion but did not reduce thirst evoked by DZX-induced hypotension. This observation prompted further investigations to determine whether hypotension-induced thirst in rats maintained on high-salt diet was dependent on residual activation of the peripheral RAS.

METHODS

Animals. Adult male Sprague-Dawley rats (Harlan Laboratories, Indianapolis, IN) weighing 275–300 g were individually housed in a temperature-controlled room (22–23°C) with a 12:12-h light-dark cycle (lights on at 7 AM). Tap water and Purina 5001 Laboratory Chow (~1% NaCl) were available ad libitum except where noted.

Effect of standard and high-NaCl diet on hypotension-induced changes in water intake, AP, heart rate, and PRA. Rats were randomly assigned to one of two dietary groups. Each diet was based on a formulation containing 0.01% Na⁺ (TD=90228, Harlan Teklad, Madison, WI) and was supplemented either with 1% NaCl (n = 9) or 8% NaCl (n = 8). Rats were placed on the respective diet on day 0 and maintained on the diet for the remainder of the experiments. Body weights did not differ between the two groups before or during these experiments. As expected (14, 18), the daily water intakes of rats fed high-NaCl diet for 2 wk were...

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Protein levels were determined by refractometry. In addition, freezing point depression using a micro-osmometer (model 3360, Advanced Instruments, Norwood, MA), and plasma free of DZX. Samples were immediately centrifuged (10,000 rpm, 15 min) after the injection of DZX. Samples were immediately centrifuged (10,000 rpm, 15 min). The first blood sample was replaced with an equal volume of isotonic saline, whereas subsequent samples were replaced with red blood cells from the previous sample. Plasma aliquots (0.1 ml) were stored at −80°C until they were analyzed for PRA as described previously (20, 27), except that incubation times for generation of ANG I were 0 and 20 min. The amount of ANG I detected at 0-min incubation was subtracted from values obtained at 20-min incubation. To facilitate comparisons, samples from animals fed one diet or the other but receiving the same treatment (e.g., DZX-25/SLN) were analyzed in the same assay.

Effect of standard and high-NaCl diet on water intake evoked by centrally administered carbachol or ANG II. In these experiments, rats were maintained on standard or high-salt diet before water intake was evoked by centrally administered carbachol or ANG II. Rats were anesthetized with halothane (2–3% in 100% O2) and placed into a stereotaxic frame with the incisor bar positioned 3.3 mm below horizontal zero. Then a 26-gauge cannula was implanted into the lateral ventricle in each rat using the following coordinates in reference to bregma: 1.5 mm caudal, 1.7 mm lateral, and 4.5 mm below the dorsal surface of the skull. Cannulas were fixed to the skull with two screws and dental acrylic and were fitted with removable obturators that extended 0.5 mm beyond the tip of the guide cannulas. Rats were treated with antibiotic (Dual-cillin; 30,000 U, im) and were fit with an infusion harness (Harvard Apparatus) that allowed the catheters to pass outside of the cage while protected by a steel spring. Experiments began 2 days later.

At least 1 h before experiments began, rats were weighed and returned to their cages. Food was removed, and a 500 ml beaker was placed with red water in the previous water bottle. The first blood sample was then injected with antibiotic (Dual-cillin; 30,000 U, im) and was immediately centrifuged (10,000 rpm, 15 min). Ten minutes later, rats were injected with DZX (10 mg/kg iv) or an equivalent volume of isotonic saline (SLN). Each rat received the three treatments in random order, with experiments conducted every other day. To further examine the effect of changing dietary Na+ content on thirst stimulated by central ANG II, an additional group of rats was maintained on a diet containing 1% NaCl (n = 6) or 8% NaCl (n = 5) as described above. Two weeks later, rats received one of three doses of ANG II. These doses of ANG II were selected from preliminary experiments performed in rats maintained on standard Purina 5001 rat chow and provided a subthreshold dose (0.25 ng), midrange dose (2.5 mg/kg DZX or SLN) and high dose (25 mg/kg DZX or SLN). Each rat received the three treatments in random order, with experiments conducted every other day.

Cumulative water intakes (±0.5 ml) were monitored every 15 min during the 90-min test, and latency to the first lick was also recorded. Urine outputs (±0.1 ml) were monitored during the 90-min test and were analyzed for Na+ and K+ concentrations (System E2A Electrolyte Analyzer, Beckman Instruments, Brea, CA). In addition, blood samples (0.4 ml) were collected from the arterial line into microcentrifuge tubes containing heparin (7 U) at baseline and 15 and 60 min after the injection of DZX. Samples were immediately centrifuged (10,000 g, 1 min). The first blood sample was replaced with an equal volume of isotonic saline, whereas subsequent samples were replaced with red blood cells from the previous sample. Plasma osmolality (P_{osmol}) was measured from two 20-µl aliquots by freezing point depression using a micro-osmometer (model 3360, Advanced Instruments, Norwood, MA), and plasma protein levels were determined by refractometry. In addition,
two-way ANOVA with repeated measures. When significant F values were obtained, one-way ANOVAs were performed at each level of dietary salt or drug treatment followed by independent t-tests or Fisher’s post hoc test, respectively. The repeated-measures variable was analyzed by paired t-tests and corrected by a layered Bonferroni analysis. PRA values were log-transformed before analysis. Plasma protein and \( P_{\text{o}} \) were analyzed by a two-way ANOVA with repeated measures, as described for MAP and HR. Latency to drink, urine volume, and urinary \( \text{Na}^+ \) and \( \text{K}^+ \) excretion were analyzed by a two-way ANOVA followed by appropriate analysis as described above. Only rats that drank during the 90-min test were included in the analysis of latency to drink. In addition, the percentage of rats that drank was compared within each diet and treatment by a Fisher’s exact test.

When water intake was plotted as a function of PRA values, the distribution of rats between groups was analyzed by a Fisher’s Exact test (chi-square). The distribution of water intakes was analyzed with reference to a horizontal line drawn through the point representing the rat maintained on 8% NaCl diet that had the lowest water intake. The distribution of PRA values was analyzed with reference to a vertical line drawn through the point representing the rat maintained on 8% NaCl diet that had the largest PRA value.

Water intakes for intracerebroventricular experiments were analyzed by a two-way ANOVA with repeated measures followed by post hoc analysis as described above for MAP and HR. Urine volume and urinary \( \text{Na}^+ \) and \( \text{K}^+ \) excretion were analyzed as described for water intakes.

**RESULTS**

Effect of standard and high-NaCl diet on hypotension-induced drinking responses, MAP, HR, and PRA values. Rats maintained on diets containing 1 or 8% NaCl ingested similar amounts of water throughout the 90-min test after systemic administration of DZx (25 mg/kg iv) (Fig. 1A). Every DZx-SLN rat drank, and the latencies to drink were similar in the two groups (Table 1). In addition, DZx-SLN significantly decreased MAP from baseline values in both groups, and MAP values were similar in rats maintained on the two diets at every time throughout the test period (Fig. 1B).

As expected, administration of DZx significantly increased PRA above baseline values in rats maintained on a diet containing 1 and 8% NaCl (Fig. 2A). However, rats fed 8% NaCl diet had markedly lower PRA values than rats fed 1% NaCl diet at baseline, 15 min, and 60 min (Fig. 2A). A scatterplot of water intakes and PRA values at 15 or 60 min for each rat is presented in Fig. 2, B and C, respectively. These figures illustrate that rats fed 8% NaCl had lower PRA values than rats fed 1% NaCl but ingested similar amounts of water.

No significant differences between DZx-SLN rats fed diets containing 1 and 8% NaCl were observed in \( P_{\text{o}} \) (Table 2) or plasma protein (\( P > 0.5 \); data not shown). Plasma protein decreased from baseline levels in hypotensive rats maintained on either diet (\( P < 0.05 \); data not shown). Furthermore, there were no differences in urine volume or in urinary \( \text{Na}^+ \) or \( \text{K}^+ \) excretion (Table 3).

**Table 1. Number of rats that drank and latencies to drink after each treatment**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Rats that Drank/ Total No. of Rats</th>
<th>Latency to Drink, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% NaCl diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZX-25 + SLN</td>
<td>9/9</td>
<td>7.5 ± 1.2</td>
</tr>
<tr>
<td>DZX-10 + CPT</td>
<td>4/9*</td>
<td>31.9 ± 10.2*</td>
</tr>
<tr>
<td>DZX-25 + CPT</td>
<td>6/8</td>
<td>19.8 ± 3.7*</td>
</tr>
<tr>
<td>8% NaCl diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZX-25 + SLN</td>
<td>8/8</td>
<td>9.9 ± 1.7</td>
</tr>
<tr>
<td>DZX-10 + CPT</td>
<td>4/8*</td>
<td>35.3 ± 14.7*</td>
</tr>
<tr>
<td>DZX-25 + CPT</td>
<td>7/8</td>
<td>17.4 ± 3.7</td>
</tr>
</tbody>
</table>

Values are means ± SE. Rats were maintained for at least 2 wk on diets containing either 1 or 8% NaCl and then infused intravenously either with isotonic saline (SLN; 1 ml/h) or captopril (CPT; 0.33 mg/min); 10 min later, diazoxide (DZX; 10 or 25 mg/kg iv) was administered. *Significant difference from DZX-25 + SLN within same diet (\( P < 0.05 \)). Only rats that drank during the 90-min test were included in the analysis of latency to drink.

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effect of CPT infusion on hypotension-induced drinking responses, MAP, HR, and PRA values in rats maintained on standard and high-NaCl diets. To determine whether the increase in water intake after DZX administration is due to increased activity of the RAS, ANG II production was blocked pharmacologically by an intravenous infusion of CPT in rats fed either 1 or 8% NaCl. DZX-25 + CPT rats maintained on a diet containing 1% NaCl ingested less water and had a longer latency to drink than DZX-25 + SLN rats (Fig. 3A, Table 1). However, these DZX-25 + CPT rats had a significantly lower MAP than DZX-25 + SLN rats throughout the test (Fig. 3B). Thus it is important to note that DZX-10 + CPT rats ingested significantly less water and had significantly longer latencies to drink than DZX-25 + SLN rats (Fig. 3A, Table 1) despite similar levels of MAP (Fig. 3B). Furthermore, a smaller percentage of DZX-10 + CPT rats drank compared with DZX-25 + SLN rats (Table 1). On the other hand, water intakes and latencies to drink were not significantly different between DZX-10 + CPT and DZX-25 + CPT rats during the 90-min test (Fig. 3A) despite substantial differences in MAP (Fig. 3B).

When CPT was given to rats maintained on a diet containing 8% NaCl, DZX-25 + CPT and DZX-10 + CPT rats both ingested significantly less water than DZX-25 + SLN rats did (Fig. 3). Indeed, a smaller percentage of DZX-10 + CPT rats drank and did so with a significantly longer latency than DZX-25 + SLN rats (Table 1). MAP of DZX-10 + CPT and DZX-25 + SLN rats were similar, although these values did differ significantly at 30 and 45 min (Fig. 3B).

A two-way ANOVA of $P_{osmol}$ revealed no significant effect of diet at any time ($P > 0.5$; Table 2). However, $P_{osmol}$ was significantly higher in DZX-25 + CPT rats than in DZX-25 + SLN and DZX-10 + CPT rats at 60 min and than in DZX-25 + CPT rats at baseline. A

Table 2. Plasma osmolality of rats maintained on diets containing 1 or 8% NaCl before treatment with DZX plus SLN or CPT

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>15 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% NaCl diet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZX-25 + SLN</td>
<td>293 ± 2</td>
<td>290 ± 1</td>
<td>293 ± 1†</td>
</tr>
<tr>
<td>DZX-10 + CPT</td>
<td>292 ± 1</td>
<td>292 ± 1</td>
<td>292 ± 1†</td>
</tr>
<tr>
<td>DZX-25 + CPT</td>
<td>290 ± 1*</td>
<td>292 ± 1*</td>
<td>301 ± 1</td>
</tr>
<tr>
<td>8% NaCl diet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZX-25 + SLN</td>
<td>295 ± 2</td>
<td>292 ± 1*</td>
<td>296 ± 1†</td>
</tr>
<tr>
<td>DZX-10 + CPT</td>
<td>291 ± 1</td>
<td>291 ± 2</td>
<td>291 ± 1†</td>
</tr>
<tr>
<td>DZX-25 + CPT</td>
<td>292 ± 2*</td>
<td>294 ± 2*</td>
<td>299 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE. Rats were maintained for at least 2 wk on diets containing 1 or 8% NaCl and then were infused intravenously either with SLN (1 ml/h) or CPT (0.33 mg/min); 10 min later, DZX (10 or 25 mg/kg iv) was administered. *Significant difference from 60 min within same treatment condition and NaCl diet ($P < 0.05$). †Significant difference from DZX-25 + CPT rats within same NaCl diet ($P < 0.05$).

Table 3. Urine volume and urinary Na⁺ and K⁺ excretion after DZX + SLN or DZX + CPT

<table>
<thead>
<tr>
<th>Group</th>
<th>Volume, ml</th>
<th>Na⁺, meq</th>
<th>K⁺, meq</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% NaCl diet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZX-25 + SLN</td>
<td>0.5 ± 0.2</td>
<td>0.09 ± 0.04</td>
<td>0.09 ± 0.05</td>
</tr>
<tr>
<td>DZX-10 + CPT</td>
<td>1.0 ± 0.2</td>
<td>0.12 ± 0.04</td>
<td>0.14 ± 0.03</td>
</tr>
<tr>
<td>DZX-25 + CPT</td>
<td>0.2 ± 0.1</td>
<td>0.01 ± 0.01</td>
<td>0.02 ± 0.01</td>
</tr>
<tr>
<td>8% NaCl diet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZX-25 + SLN</td>
<td>0.7 ± 0.4</td>
<td>0.22 ± 0.11</td>
<td>0.06 ± 0.03</td>
</tr>
<tr>
<td>DZX-10 + CPT</td>
<td>1.8 ± 0.7</td>
<td>0.40 ± 0.16</td>
<td>0.11 ± 0.04</td>
</tr>
<tr>
<td>DZX-25 + CPT</td>
<td>1.1 ± 0.3a</td>
<td>0.16 ± 0.06a</td>
<td>0.06 ± 0.01</td>
</tr>
</tbody>
</table>

Values are means ± SE. Rats were maintained for at least 2 wk on diets containing 1 or 8% NaCl and then were infused intravenously either with SLN (1 ml/h) or CPT (0.33 mg/min); 10 min later, DZX (10 or 25 mg/kg iv) was administered. *Significant difference from rats maintained on 1% NaCl diet within same treatment condition ($P < 0.05$).
two-way ANOVA of plasma protein revealed no significant effect of diet (P > 0.5) or treatment condition (P > 0.1; data not shown). However, plasma protein values significantly decreased from baseline values at 15 and 60 min in each treatment condition and in both 1 and 8% NaCl diets (P < 0.05; data not shown). There was no significant effect of CPT on urine volume or urinary Na⁺ and K⁺ excretion (Table 3), and diet had no effect on K⁺ excretion (Table 3). However, there was an effect of diet on urinary volume and Na⁺ excretion by DZX-25 + CPT rats (Table 3).

Effect of standard and high-NaCl diet on water intake evoked by centrally administered carbachol, ANG II, and isotonic saline. In these experiments, rats were fed 1 or 8% NaCl for at least 2 wk and then received an injection of carbachol, ANG II, or isotonic saline into the lateral cerebral ventricle. Water intake in response to carbachol was not significantly different between rats in the two groups (Fig. 4A), whereas rats ingested significantly more water in response to 2.5 ng ANG II when the diet contained 8% NaCl instead of 1% NaCl (Fig. 4A). Injection of isotonic saline had no effect in either group (Fig. 4A). In addition, there were no significant differences in urinary volume or in urine Na⁺ and K⁺ excretion in response to carbachol, ANG II, or SLN between rats maintained on 1 and 8% NaCl diets (data not shown).

Because rats fed 8% NaCl diet ingested more water in response to 2.5 ng ANG II than those fed 1% NaCl diet, additional experiments were performed to further evaluate this effect. With each dose of ANG II tested, rats fed 8% NaCl ingested significantly more water than rats fed 1% NaCl (Fig. 4B). In addition, water intakes of both groups of rats increased in a dose-dependent manner (P < 0.05). Rats maintained on 8% NaCl diet excreted significantly more Na⁺ than rats maintained on 1% NaCl diet in response to 0.25 and 25 ng ANG II (P < 0.05; data not shown).

DISCUSSION

Increases in dietary salt are known to reduce basal renin secretion (12) and blunt stimulated increases in renin secretion (15, 16, 28). Consequently, rats maintained on high-NaCl diet should have smaller increases in renin secretion during arterial hypotension and therefore smaller drinking responses, because the induced thirst appears to be dependent on activation of the peripheral RAS (2–4, 8, 11, 26). The present findings demonstrate that an elevation in dietary NaCl did markedly attenuate the increase in PRA stimulated by DZX-induced hypotension in rats. However, increased dietary salt did not affect the latency to drink or the induced increase in water intake. These surprising
results provoked further consideration of the stimulus for thirst under the present experimental conditions. These findings cannot be explained by differences in the degree of hypotension between the two groups or by differences in $P_{\text{osmol}}$, plasma protein, or urinary output. Nor is it likely that DZX-treated rats maintained on high-salt diet were less thirsty but nonetheless drank more water because ingested water leached NaCl from gastric chyme en route to the intestines, thereby making the water less hydrating. After all, the latencies to drink of these animals were similar to those of rats maintained on standard diet, which suggests that maintenance on high-salt diet does not invariably lead to the overconsumption of water.

An alternative hypothesis is that drinking elicited by DZX-evoked hypotension in rats maintained on a high-salt diet occurs independently of the peripheral RAS. To test this notion, ANG II production was blocked pharmacologically by CPT, an angiotensin-converting enzyme inhibitor, in DZX-treated rats maintained on high-salt diet. Previous studies have demonstrated that CPT treatment markedly attenuates hypotension-induced thirst in rats fed standard laboratory diet (2–4, 11). The present findings confirm and extend these observations by indicating that the infusion of CPT nearly eliminated the increase in water intake and also greatly lengthened the latency to drink in rats maintained on a diet containing 1% NaCl. A more striking effect, however, was that the infusion of CPT similarly inhibited drinking behavior in rats maintained on high-salt diet. Although CPT may have other actions in addition to the inhibition of ANG II synthesis (29), those actions probably are not responsible for its suppressive effect on hypotension-evoked thirst because replacement of circulating ANG II levels by an intravenous infusion of ANG II has been reported to restore drinking behavior in DZX + CPT rats (2). Furthermore, CPT likely did not inhibit hypotension-evoked thirst by generally disrupting drinking behavior, because CPT administered alone or in combination with DZX does not interfere with drinking stimulated by intravenous infusion of hypertonic saline (2, 19) or ANG II (2, 24). Moreover, a high dose of CPT that blocked drinking stimulated by renin or ANG I administered into the lateral ventricle did not affect the increase in water intake that occurred when ANG II was given into the lateral ventricle or peripherally (5). These results indicate that CPT treatment does not interfere with the mechanisms necessary for the diuretic actions of peripheral ANG II. Thus drinking behavior during DZX-evoked hypotension in rats maintained on diets containing either 1 or 8% NaCl appears to be mediated by the peripheral RAS despite large differences in PRA.

The precise relation between peripheral ANG II and thirst in rats has never been defined under conditions of arterial hypotension. Because circulating ANG II was not measured in the present experiments, it is not even certain that the relatively low PRA values observed in rats fed high-salt diet reflect a suppressive effect of dietary salt on circulating ANG II levels. However, others have reported that circulating ANG II levels do decrease in response to increased dietary salt (7, 13). If PRA values actually reflect circulating levels of ANG II in the present animals, then the modest increase in PRA values in DZX-treated rats maintained on high-salt diet probably is not large enough to stimulate thirst in rats maintained on a standard salt diet. Thus, assuming that circulating ANG II does provide the stimulus of thirst in DZX-treated rats maintained on high-salt diet and that circulating levels of ANG II are much lower in these animals than in rats...
maintained on standard diet, then the drinking response of rats fed 8% NaCl diet would appear to reflect an increase in the dipsogenic potency of peripheral ANG II.

Interestingly, rats fed 8% NaCl ingested much more water than rats fed 1% NaCl when ANG II, but not carbachol, was injected into the lateral cerebral ventricle. In fact, rats fed a high-salt diet drank as much water when given 0.25 ng of ANG II centrally as rats fed a 1% NaCl diet and given 2.5 ng ANG II. These observations suggest a 10-fold increase in the dipsogenic potency of central ANG II in rats fed a high-salt diet. Whether the same is true of circulating ANG II awaits further investigation. In this regard, we did not infuse ANG II intravenously in the present experiments because the obtained results may have been very difficult to interpret. Intravenous ANG II stimulates the ingestion of water but also provides an inhibitory signal for thirst due to the associated increase in AP (1, 6, 19, 24, 25). Because increases in dietary salt enhance the pressor activity of acutely administered peripheral ANG II (22, 23) and also alter baroreflex function (9, 10), an increased dipsogenic potency of intravenous ANG II in rats fed a high-salt diet would be confounded by cardiovascular changes and their impact on water intake.

The mechanism(s) underlying the enhanced dipsogenic response to the circulating ANG II may consist of, but are not limited to, an enhanced cellular response to peripheral ANG II and/or an enhanced response of the central neural circuits mediating ANG II-induced water intake. Consistent with these possibilities, it is interesting to note that the percent change in PRA values in response to DZX-induced hypotension is not significantly different in rats maintained on standard and high-salt diets. Therefore, it is possible that the change in circulating ANG II levels relative to circulating basal levels is more relevant as a stimulus of thirst than the absolute values of circulating ANG II.

Clearly, further investigation is needed to address these issues.

In summary, the present findings demonstrate that increases in dietary salt intake markedly blunt hypotension-induced increases in PRA yet do not affect the induced thirst. Furthermore, hypotension-induced thirst appears to be mediated by the peripheral RAS in rats maintained on high-salt diet, as blockade of ANG II synthesis by CPT attenuated the increase in water intake. These results suggest that increasing dietary salt intake is associated with enhanced dipsogenic effects of circulating ANG II. Rats fed a high-salt diet were not more responsive to carbachol administered centrally, indicating that increased dietary salt does not enhance thirst in response to all treatments. Collectively, these observations suggest that hypotension-induced thirst in rats fed high-salt diet remains dependent on activation of the peripheral RAS, despite markedly low PRA. The basis of the elevated water intake in these conditions remains to be determined. More generally, it seems clear that investigations in which dietary salt intake is altered to affect the activity of the peripheral RAS must allow for the possibility that postsynaptic changes in ANG II-sensitive neurons or pathways may compensate for induced changes in circulating ANG II levels.

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