Reset of the osmotic threshold for vasopressin in rats fed a low NaCl, K-free diet

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Activation of the renin-angiotensin system induced by feeding a low NaCl, K-free (LS) diet is associated with polydipsia and a chronic reduction in effective plasma osmolality (eP\text{\textsubscript{osm}}). We have recently shown that converting enzyme inhibition with enalapril (EP) abolishes polydipsia. The present study was designed to test the hypothesis that the osmotic threshold for vasopressin is reset in rats fed the LS diet and to examine the effect of EP on ambient and osmotically stimulated plasma vasopressin levels (P\text{\textsubscript{AVP}}). Animals were fed the LS diet or a control salt diet and treated with vehicle or the lowest dose of EP sufficient to prevent polydipsia (7.5 mg · kg\textsuperscript{-1} · day\textsuperscript{-1}) in rats fed the LS diet. P\text{\textsubscript{AVP}} and eP\text{\textsubscript{osm}} were measured under ambient conditions and after osmotic loading. Urine osmolality (U\text{\textsubscript{osm}}) was measured under ambient conditions and after water loading. The chronic reduction in eP\text{\textsubscript{osm}} in LS rats was associated with the excretion of a U\text{\textsubscript{osm}} 1–2 times greater than the corresponding P\text{\textsubscript{osm}}. P\text{\textsubscript{AVP}} similar to controls (LS, 2.27 ± 1.08 vs. control, 1.19 ± 0.22 pg/mL) and the ability to excrete a water load. Following osmotic loading, eP\text{\textsubscript{osm}} and P\text{\textsubscript{AVP}} increased significantly and similarly in both LS and control rats. EP administration had no effect on water intake, ambient eP\text{\textsubscript{osm}} and P\text{\textsubscript{AVP}}, and the AVP response to osmotic loading in rats fed the control diet. EP prevented polydipsia in LS rats, however it had no significant effect on ambient or osmotically stimulated P\text{\textsubscript{AVP}} or eP\text{\textsubscript{osm}}. These results provide evidence that the osmotic threshold for AVP is reset in rats fed the LS diet and although converting enzyme inhibition has a profound effect on water intake, angiotensin II does not appear to be the only variable affecting the osmotic threshold for AVP release.

Key words: arginine vasopressin, antidiuretic hormone, osmotic threshold, plasma osmolality, rats, converting enzyme inhibition, angiotensin II, thirst.


L’activation du système rénine–angiotensine, induite par une diète sans K à faible teneur en NaCl (FS), est associée à la polydipsie et à une réduction chronique de l’osmolalité plasmatique effective (P\text{\textsubscript{osm}}.eff). Nous avons récemment montré que l’inhibition des enzymes de conversion par l’énalapril (EP) élimine la polydipsie. La présente étude a été conçue pour vérifier l’hypothèse que le seuil osmotique pour la vasopressine est rajusté chez les rats soumis à une diète FS, et elle examine l’effet de l’EP sur les taux de vasopressine plasmatique (P\text{\textsubscript{AVP}}) stimulé osmotiquement et ambiant. Les animaux ont reçu une diète sódée témoin ou une diète FS, et ils ont été traités avec un véhicule ou la plus faible dose d’EP suffisante pour prévenir la polydipsie (7.5 mg · kg\textsuperscript{-1} · jour\textsuperscript{-1}) chez les rats nourris avec la diète FS. La P\text{\textsubscript{AVP}} et la P\text{\textsubscript{osm}}.eff ont été déterminées dans des conditions ambiantes et après une charge osmotique. L’osmolalité urinaire (U\text{\textsubscript{osm}}) a été déterminée dans des conditions ambiantes et après une charge aquéuse. La réduction chronique de P\text{\textsubscript{osm}}.eff chez les rats FS a été associée à l’excration d’une U\text{\textsubscript{osm}} 1–2 fois plus élevée que la P\text{\textsubscript{osm}} correspondante, à une P\text{\textsubscript{AVP}} similaire à celle des témoins (LS, 2.27 ± 1.08 vs. témoin, 1.19 ± 0.22 pg/mL) et à la capacité d’excréter une charge d’eau. Après une charge osmotique, la P\text{\textsubscript{osm}}.eff et la P\text{\textsubscript{AVP}} ont augmenté significativement et simultanément tant chez les rats témoins que chez les rats FS. L’administration d’EP n’a pas eu d’effet sur l’apport d’eau, ni sur la P\text{\textsubscript{osm}}.eff et la P\text{\textsubscript{AVP}} ambiantes, ni sur la réponse de l’EP à la charge osmotique chez les rats nourris avec la diète témoin. L’EP a prévenu la polydipsie chez les rats FS, mais elle n’a pas eu d’effet significatif sur la P\text{\textsubscript{AVP}} ou la P\text{\textsubscript{osm}}.eff stimulée osmotiquement ou ambiant. Ces résultats mettent en évidence que le seuil osmotique pour l’AVP est rajusté chez les rats soumis à une diète FS, et bien que l’inhibition des enzymes de conversion ait un effet considérable sur l’apport d’eau, l’angiotensine II ne semble pas être le seul paramètre affectant le seuil osmotique de la libération d’AVP.

Mots clés : arginine vasopressine, hormone antidiurétique, seuil osmotique, osmolalité plasmatique, rats, inhibition des enzymes de conversion, angiotensine II, soit.

[Traduit par la rédaction]

Introduction

Previous work has established that acute increases in blood-borne angiotensin II (ANG II) increases water intake, vasopressin (AVP) release and blood pressure in experimental animals (Fitzsimons 1985; Franci et al. 1989; Johnson et al. 1986; Mann et al. 1987). Also, acute administration of ANG II has been shown to induce thirst, stimulate release of AVP, and to increase the slope of the P\text{\textsubscript{osm}} versus P\text{\textsubscript{AVP}} relationship in humans (Phillips et al. 1985; Wade et al. 1986). What is the evidence that endogenous ANG II has a significant effect on the regulation of water intake and vasopressin release?

Although endogenous ANG II has no effect on basal water intake, it is the single controlling factor accounting for increased water intake in animals in which there is activation of the renin–angiotensin system induced by feeding a low NaCl, K-free diet (Saikaley et al. 1986; McKay et al. 1990), and in animals with vitamin D-induced chronic hypercalcaemia (Mathur et al. 1990). In addition, ANG II largely accounts for increased water intake in response to dehydration (Franci et al. 1989). However, there is no evidence that chronic changes in endogenous ANG II alters the “osmotic threshold” of AVP release.

In previous studies, we demonstrated that the chronic reduction in effective plasma osmolality (eP\text{\textsubscript{osm}}) in rats fed a low
Animals, diets, and the converting enzyme inhibitor

Experiments were performed in 70 male Sprague-Dawley rats (Charles River, Quebec) weighing between 253 and 450 g. The animals were housed in individual cages and allowed free access to food and water. The LS and control salt diets were prepared in our laboratory by the addition of a salt mixture to a basal "electrolyte-free" diet (modified TD72105, Teklad Test Diets, Madison, WI) as previously described (Saikaley et al. 1986; McKay et al. 1990). Rats drank water containing enalapril (EP, provided by Merck-Frosst Canada, Montréal) dissolved in 0.1% ethanol or the vehicle alone, i.e., 0.1% ethanol. The concentration of enalapril in the drinking water was adjusted to the water intake and body weight of the animal (measured daily) to achieve the daily dose of 7.5 mg/kg.

Protocol

Prior to the study, all of the animals were fed the control diet for 2 days, at which time they were randomly divided into two groups. Half of the rats were fed the LS diet, the other rats continued to consume the control diet. Water (containing 0.1% ethanol) consumption and body weight were measured at the same time each day. After 3 days (study days 1–3), half of the animals in each group were treated with EP until the end of the study. Water consumption was recorded on days 4 and 5. On day 6, at 10:00 h, a sample of spontaneously voided urine was collected and a water load (2 mL/100 g BW) was administered by gavage. The animals were placed in metabolic cages and urine was collected for the next 4 h.

At the end of the study on day 7 at 10:00 h, to obtain basal values of $P_{AVP}$ and $eP_{osm}$, half the animals (unstressed) were decapitated. Free-flowing trunk blood was collected into one set of chilled tubes containing EDTA for measurement of AVP and a second set of tubes containing heparin for measurement of $P_{creatinine}$, urea, glucose, and electrolytes. In the remaining animals on day 7, to determine the response to osmotic stimulation, Na$_2$SO$_4$ (1000 mosmol/kg H$_2$O) was administered intraperitoneally (2 mL/100 g BW) 30 min before decapitation. Samples for AVP and osmolality, serum chemistries, and electrolytes were obtained as above. These animals were also subjected to the previous measurements of urine osmolality and water loading experiments as described above.

Analytical methods

The osmolality of heparinized plasma and urine samples was measured using a freezing point depression osmometer ($\mu$Osmette, model 5004, Precision Science, MA). Plasma [Na] was measured using an ion-sensitive electrode (Na K Analyzer, model 614, Ciba Corning, Medfield, Mass.) and plasma [Cl] by electrotitration (Chloride Analyzer, model 965, Ciba Corning). Plasma urea, glucose, and creatinine concentrations were measured using an AutoAnalyzer (Kodak Ektachem, model 700, Kodak Industries, Rochester, NY). Plasma vasopressin was measured by radioimmunoassay assay (Dr. Daniel Bichet, Hôpital du Sacré-Coeur, Montréal, Québec (Bichet et al. 1986). The AVP assay laboratory was blind to the source of each sample.

Calculations and statistical analysis

All quantitative results are expressed as the mean ± SEM. Effective $P_{osm}$ was calculated as:

$$eP_{osm} = P_{osm} - [(\text{urea}) \text{ (mM)} + (\text{glucose}) \text{ (mM)}]$$

When only two treatment groups were involved in the experiment, Student's t-test for paired or unpaired data was used to assess the statistical significance of the difference between the means. In all other cases, one-way analysis of variance with the least significant difference multiple comparison test was used to determine the statistical significance of differences between group data. To determine the separate effects of diet, drug, and (or) osmotic loading, the results were analyzed by multivariate analysis of variance. A probability value of $p < 0.05$ was considered to be statistically significant.

Results

Effect of enalapril on water intake

In rats fed the LS diet, water intake increased significantly on the third day of study (control, 9.4 ± 0.24 (n = 30), LS, 14.7 ± 1.03 (n = 26) mL/100 g BW per day, $p < 0.01$). After initiation of EP treatment on day 4, water intake decreased only in the LS rats receiving EP, while water intake remained elevated in the LS rats given the vehicle. There was no change in water intake in rats fed the control diet in response to EP administration. The results were virtually the same on day 5. Average water intake calculated for days 4 and 5 of the study is summarized in Fig. 1. Multivariate analysis of variance indicated that the LS diet stimulates water intake and that EP has an effect on water intake only in rats fed the LS diet.

Plasma osmolality and concentrations of Cl, Na, creatinine, urea, and glucose in rats fed the LS or control diet treated with or without EP are summarized in Table 1. $P_{osm}$ was significantly reduced in rats fed the LS diet given vehicle compared with both groups of rats fed the control salt diet. Although...
Table 1. Plasma osmolality and Cl, Na, creatinine, urea, and glucose concentrations in rats fed the control salt or low NaCl, K-free diet (LS) in the presence and absence of enalapril (EP) for 7 days

<table>
<thead>
<tr>
<th>Plasma</th>
<th>Control</th>
<th>Control + EP</th>
<th>LS</th>
<th>LS + EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{osm}$, mosmol/kg H$_2$O</td>
<td>300±1.2</td>
<td>301±4.0</td>
<td>290±1.0*</td>
<td>296±2.0</td>
</tr>
<tr>
<td>Cl, mM</td>
<td>105±1.1</td>
<td>111±2.4**</td>
<td>98±1.7*</td>
<td>112±1.0**</td>
</tr>
<tr>
<td>Na, mM</td>
<td>139±0.9</td>
<td>139±2.2</td>
<td>136±0.8</td>
<td>135±0.4</td>
</tr>
<tr>
<td>Creatinine, μM</td>
<td>23±2.4</td>
<td>23±1.5</td>
<td>33±1.7*</td>
<td>37±4.0*</td>
</tr>
<tr>
<td>Urea, mM</td>
<td>5.5±0.31</td>
<td>7.0±0.36</td>
<td>5.3±0.26</td>
<td>13.4±1.83**</td>
</tr>
<tr>
<td>Glucose, mM</td>
<td>9.6±0.51</td>
<td>8.7±0.26</td>
<td>10.1±0.58</td>
<td>9.0±0.43</td>
</tr>
</tbody>
</table>

Note: Values are means ± SE. Values in parentheses are the number of rats. 

*p < 0.05 vs. control, control + EP. 

**p < 0.05 vs. vehicle treated same diet.

Table 2. Effect of diet and enalapril on random urine osmolality and excretion of a water load

<table>
<thead>
<tr>
<th>Urine</th>
<th>Control</th>
<th>Control + EP</th>
<th>LS</th>
<th>LS + EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>$U_{osm}$ (mosmol/kg H$_2$O)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambient</td>
<td>1001±75.9</td>
<td>762±41.7**</td>
<td>590±39.2</td>
<td>533±54.8*</td>
</tr>
<tr>
<td>After waterload</td>
<td>298±20.2</td>
<td>308±13.0</td>
<td>238±14.3*</td>
<td>228±26.6*</td>
</tr>
<tr>
<td>% waterload excreted</td>
<td>84±4.3</td>
<td>98±4.1</td>
<td>89±5</td>
<td>127±8.1***</td>
</tr>
</tbody>
</table>

Note: Values are means ± SE. Values in parentheses are the number of rats. EP, enalapril; LS, low NaCl, K-free.

*p < 0.05 vs. control, control + EP. 

**p < 0.05 vs. vehicle treated same diet. 

***p < 0.05 vs. all other groups.

$P_{osm}$ increased in LS rats treated with EP, the measured values still overlap with those measured in LS rats given the vehicle. Plasma [Cl] was significantly reduced in rats fed the low salt diet receiving vehicle compared with all the other treatment groups. Although there was an increase in plasma [Cl] in rats fed the control salt diet in response to EP, multivariate analysis of variance indicated there was interaction between dietary treatment and EP such that the effect on plasma [Cl] was much greater in rats fed the LS diet. Although plasma [Na] tended to be approximately 3 mM/L lower in rats fed the LS diet, there were no statistically significant differences in plasma [Na], and EP had no effect on this variable. Feeding the LS diet was associated with an increase in plasma creatinine concentration, and multivariate analysis of variance indicated that treatment with EP did not have a significant effect in either dietary group. As in the case of water intake, there was interaction between the LS diet and EP on plasma concentration of urea, which increased only in rats fed the LS diet treated with EP. There were no significant differences in plasma glucose concentration among the experimental groups.

Ambient $U_{osm}$ and the results of water loading experiments are summarized in Table 2. Ambient $U_{osm}$ in both dietary groups was higher ($p < 0.05$) than the corresponding value of $P_{osm}$ (Table 1). In rats fed the LS diet, ambient $U_{osm}$ was lower compared with the control rats. Treatment with EP had no effect on ambient urine osmolality in rats fed the LS diet, however, ambient urine osmolality was lower in rats fed the control salt diet treated with EP compared with control rats given the vehicle.

Following administration of a water load by gavage, the osmolality of a pooled urine sample collected over the subsequent 4 h was reduced in all of the rats compared with the ambient $U_{osm}$. In rats fed the control diet, $U_{osm}$ of this sample was equivalent to the corresponding value of $P_{osm}$ (Table 1). Failure to reduce $U_{osm}$ below $P_{osm}$ can be attributed to mixture of urine with a high osmolality prior to administration of the water load (Table 2). However, in rats fed the LS diet, $U_{osm}$ of this sample was significantly lower than $P_{osm}$ measured in the same animal ($p < 0.001$). Effective dilution of the urine was more evident in rats fed the LS diet since $U_{osm}$ before administration of the water load was significantly less than that measured in the control rats (Table 2). As in the case of the ambient urine sample, $U_{osm}$ after the water load was lower in rats fed the LS diet compared with the controls and EP treatment had no effect in either dietary group. As shown in Table 2, rats fed the LS diet given the vehicle excreted a similar percentage of the administered water load compared with the control rats. In addition, rats fed the LS diet treated with EP excreted a larger percentage of the administered volume.

Vasopressin measurements

Effective $P_{osm}$ and corresponding AVP measurements under ambient conditions and after osmotic loading in rats fed the LS or control diet treated with or without EP are summarized in
Figs. 2 and 3, respectively. Under ambient conditions \( \text{efP}_{\text{osm}} \) was significantly lower in rats fed the LS diet given vehicle compared with rats fed the control diet with or without EP (Fig. 2). It is clear that EP had no effect on \( \text{efP}_{\text{osm}} \) in rats fed the control diet. \( \text{efP}_{\text{osm}} \) increased in LS rats treated with EP to such an extent that the measured values were no longer different from those measured in rats fed the control diet. However, the difference in \( \text{efP}_{\text{osm}} \) between rats fed the LS diet treated with or without EP was not statistically significant.

Despite the significant reduction in \( \text{efP}_{\text{osm}} \), rats fed the LS diet given vehicle had AVP measurements similar to those measured in rats fed the control diet (Fig. 2). The mean values under ambient conditions ranged from 1.19 to 2.32 pg/mL in the four treatment groups. Administration of EP had no effect on AVP levels in either dietary group.

Administration of the intraperitoneal osmotic load led to a significant increase in \( \text{efP}_{\text{osm}} \) in all four groups (Fig. 3) \( (p < 0.05) \). Multivariate analysis of variance showed that the measured values were similar and unaffected by dietary or EP treatment. As illustrated in Fig. 3, AVP levels increased significantly in all four groups by the osmotic load (vs. ambient ANOVA with eight groups, \( p < 0.05 \)) and there was no effect of diet or EP on this variable (multivariate ANOVA).

Discussion

The results of the present study provide evidence that AVP release is reset to a lower value of \( \text{efP}_{\text{osm}} \) in rats fed a LS diet. We have established that \( \text{efP}_{\text{osm}} \) is reduced, that AVP is present in plasma, and that the animals elaborate a urine with an osmolality greater than plasma. In addition, evidence is provided that AVP can be stimulated by osmotic loading, and suppressed by water loading to permit the excretion of a urine with an osmolality significantly less than plasma.

The factors affecting AVP release have been reviewed elsewhere (Berl and Schrier 1992; Bichet et al. 1992; Peterson 1989; Robertson 1991). Conceptually, the “osmotic threshold” can be defined as that value of \( \text{efP}_{\text{osm}} \) at which \( P_{\text{AVP}} \) is no longer sufficient to promote free water reabsorption by the kidney. Practically it has been defined as the value of \( \text{efP}_{\text{osm}} \) at which \( P_{\text{AVP}} \) can no longer be detected by radioimmunoassay, which in the present study is 0.5 pg/mL (Bichet et al. 1986). The osmotic threshold is several milliosmoles per kilogram of \( H_2O \) below the steady-state or ambient \( \text{efP}_{\text{osm}} \). In the present study a change in the osmotic threshold has been inferred from a sustained reduction in \( \text{efP}_{\text{osm}} \) at which \( P_{\text{AVP}} \) is clearly within the range of values measured in control animals.

It is well established that the osmotic threshold for AVP release is relatively constant in an individual and that it can be
affected by several factors, e.g., reduced effective circulating volume (neurogenic pathways involving circulatory baro- and volume receptors) and pregnancy (hormonal via human chorionic gonadotropin, Davison et al. 1988). In most cases of marked extracellular fluid (ECF) volume contraction, altered baroreceptor activity and activation of the renin–angiotensin system coexist, making it difficult to assess the separate effects of each pathway on AVP release. For example, in chronic chloride depletion metabolic alkalosis, there is a reduction in $eP_{osm}$, primary polydipsia, and reset of the osmotic threshold for AVP demonstrated by regression analysis of the relation between $P_{osm}$ and $P_{AVP}$ (Peterson et al. 1988). Associated with these changes was a marked rise in plasma renin activity. As mentioned previously, although acute administration of ANG II can stimulate release of AVP and has been shown to increase the slope of the $P_{osm}$ versus $P_{AVP}$ relationship in humans (Phillips et al. 1985), there is no evidence that chronic changes in endogenous ANG II alter the osmotic threshold of AVP release.

Is it possible that chronic stimulation of AVP by ANG II mediates the reduction in $eP_{osm}$ in rats fed the low salt diet? One of the aims of the present study was to test the hypothesis that increased ANG II mediates the chronic reduction in $eP_{osm}$ in rats fed the LS diet. The lowest effective dose of EP was chosen to minimize the confounding effect of hypotension on AVP release. Although manipulation of the angiotensin system by the converting enzyme inhibitor in the present study again demonstrates the central importance of endogenous ANG II on water intake, the results clearly show that ANG II is not the only factor involved in the regulation of AVP.

Following administration of EP to rats fed the LS diet there was a slight but not statistically significant increase in $eP_{osm}$. It is possible that increased ANG II in rats fed the LS diet given the vehicle does stimulate AVP and mediates the reduction in $eP_{osm}$: however, after administration of EP to rats fed the LS diet, drug-induced hypotension (Mimran et al. 1988) via neurogenic pathways leads to sustained stimulation of AVP, thereby obscuring the effect of reduced ANG II. It is clear that the effect of EP treatment to prevent polydipsia in these animals is unaffected by the presence of drug-induced hypotension. On the other hand, it is possible that a chronic increase in ANG II does not have a major effect on the control of AVP. There is other evidence that suggest different regulatory mechanisms for thirst and AVP. For example, although the reduction in $P_{osm}$ that occurs in rats fed the LS diet follows the same time course as the increase in water intake, stereotoxic lesion of the subfornical organ prevents polydipsia but does not prevent the significant reduction in $P_{osm}$ (Saikaly et al. 1986). In addition, in hypercalcemic animals, increased water intake, which can be prevented using a converting enzyme inhibitor, occurs in the absence of any change in $eP_{osm}$ (Mathur et al. 1990).

Is it possible that redistribution of Na from ECF to intracellular fluid (ICF) secondary to dietary-induced loss of K is responsible for the reset of the osmotic threshold for AVP release in rats fed the LS diet? It has been suggested that cellular redistribution of Na in K-depleted subjects can contribute to the presence of hyponatremia (Laragh 1954; Fichman et al. 1971). In this regard the following should be noted, redistribution of Na into cells to replace lost K will not result in a reduction in body fluid osmolality. A sustained reduction in effective osmolality of body fluids in subjects who can dilute and concentrate their urine normally must involve an alteration in the driving forces for AVP release, i.e., “reset of the osmotic threshold.” In one of the studies (Fichman 1971), K depletion was induced by administration of a thiazide diuretic, which caused a significant degree of effective circulating volume depletion and metabolic alkalosis. Most of these patients were also polydipsic. Because thiazide diuretics impairs diluting ability but not urine concentrating ability, they are much more likely to cause hyponatremia. In addition, volume depletion of the degree noted in this study is capable of causing altered AVP release via baroreceptor and volume receptor pathways. In a more recent study by Friedman et al. (1989), the patients who developed hyponatremia following a single dose of a thiazide diuretic were polydipsic and significantly hypoosmotic before the study began. High water intake in the presence of the thiazide caused more marked hyponatremia, which could have been prevented if water intake had been restricted. The partial correction of hyponatremia in six edematous patients with long standing liver or cardiac disease by the administration of KCl does represent the exchange of ICF Na for ECF K, but may not have reflected a change in $eP_{osm}$, which was not measured. In this study, ECF osmolality had to have been increased initially due to the administration of K orally (20% solution). The results of these studies although interesting can not be compared with those of the present study. The sustained reduction in effective circulating volume in patients with cirrhosis or congestive heart failure has been shown to be the major factor contributing to AVP release (i.e., sustained hypotonicity) in these clinical settings (Bichet et al. 1986; Bichet et al. 1992). In summary, there is no evidence that redistribution of Na from ECF to ICF secondary to K loss per se can cause reset of the osmotic threshold. A sustained reduction in $eP_{osm}$ in animals capable of diluting and concentrating urine normally, as demonstrated in the present study, must be due to altered release of AVP and not to distribution of Na into the intracellular compartment.

Why did treatment of rats fed the LS diet with EP cause an increase in plasma urea concentration in the absence of a further increase in plasma creatinine concentration? Previous studies have shown that lower doses of converting enzyme inhibitors (e.g., enalapril, 1, 3, and 6 mg·kg⁻¹·day⁻¹), stimulate water intake in rats fed a control diet, while higher doses of 20 and 40 mg·kg⁻¹·day⁻¹ are not dipogenic (Rowland and Fregly 1988; McKay and Peterson 1990). However, the dose of 40 mg·kg⁻¹·day⁻¹ was associated with renal insufficiency in rats fed the LS diet and the data indicated the existence of hypotension in both dietary groups. Since changes in baroreceptor and volume receptor activity can alter AVP release, we determined the minimal dose of the converting enzyme inhibitor sufficient to prevent polydipsia in rats fed the LS diet. The dose of 7.5 mg·kg⁻¹·day⁻¹ prevented polydipsia in rats fed the LS diet, and had no significant effect on water intake, plasma creatinine and urea concentrations, and effective $P_{osm}$ in rats fed the control diet. The results of the present study using larger numbers of animals revealed that feeding the LS diet was associated with increased plasma creatinine concentration (decreased glomerular filtration rate (GFR)), and the lower dose of EP did not worsen renal function. The association between dietary K depletion and reduced GFR is well known (Gutsche et al. 1984). Despite
the fact that plasma creatinine concentration was increased in rats fed the LS diet, plasma urea concentration was elevated only in the LS rats treated with the converting enzyme inhibitor. It may be that polyuria in the rats fed the LS diet given the vehicle tended to normalize plasma urea concentration by diminishing urea reabsorption in these polydipsic animals with renal insufficiency. After initiation of EP treatment and the cessation of polydipsia and consequently polyuria, urea reabsorption would return to normal thus allowing the plasma urea concentration to increase. These changes were not observed in rats fed the control diet, which had no evidence of renal insufficiency.

The significant decrease in ambient U_{osm} in control rats treated with EP may be due to increases in medullary blood flow secondary to converting enzyme inhibition (Cupples et al. 1988). Random U_{osm} in rats fed the LS diet was significantly lower than control rats and EP had no further effect. The renal concentrating defect associated with K depletion has been shown to be due to defective thick ascending limb NaCl reabsorption (Gutsche et al. 1984; McKay and Peterson 1991).

In conclusion, the results of the present study provide evidence that AVP release is reset to a lower value of eff_{osm} in rats in which the renin–angiotensin system is activated by feeding a low NaCl, K-free diet. Although converting enzyme inhibition has a profound effect on water intake, the data indicate that ANG II is not the only variable affecting the osmotic threshold for AVP release.

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