Effect of primary polydipsia on aquaporin and sodium transporter abundance

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Cadnapaphornchai, Melissa A., Sandra N. Summer, Sandor Falk, Joshua M. Thurman, Mark A. Knepper, and Robert W. Schrier. Effect of primary polydipsia on aquaporin and sodium transporter abundance. Am J Physiol Renal Physiol 285: F965–F971, 2003. First published July 22, 2003; 10.1152/ajprenal.00085.2003.—Chronic primary polydipsia (POLY) in humans is associated with impaired urinary concentrating ability. However, the molecular mechanisms responsible for this finding have not been elucidated. The purpose of this study was to examine the effect of chronic primary POLY on water metabolism and renal aquaporin (AQP) water channels and sodium and urea transporter abundance in rats. Primary POLY was induced in male Sprague-Dawley rats by daily administration of 15 g powdered rat chow mixed in 100 ml water for 10 days. Control rats (CTL) received 15 g powdered rat chow per day and ad libitum drinking water. Rats were studied following this period before further intervention and with a 36-h period of water deprivation to examine maximal urinary concentrating ability. At baseline, POLY rats demonstrated significantly greater water intake (100 ± 1 vs. 22 ± 2 ml/day, P < 0.0001) and urinary output (80 ± 1 vs. 11 ± 1 ml/day, P < 0.0001) and decreased urinary osmolality (159 ± 13 vs. 1,365 ± 188 mosmol/kgH2O, P < 0.001) compared with CTL rats. These findings were accompanied by decreased inner medulla AQP-2 protein abundance in POLY rats compared with CTL rats before water deprivation (76 ± 2 vs. 100 ± 7% CTL mean, P < 0.007). With water deprivation, maximal urinary osmolality was impaired in POLY vs. CTL rats (2,404 ± 148 vs. 3,286 ± 175 mosmol/kgH2O, P < 0.0005). This defect occurred despite higher plasma vasopressin concentrations and similar medullary osmolalities in POLY rats. In response to 36-h water deprivation, inner medulla AQP-2 protein abundance was decreased in POLY rats compared with CTL rats (65 ± 5 vs. 100 ± 5% CTL mean, P < 0.0006). No significant differences were noted in renal protein abundance of either AQP-3 or AQP-4 or sodium and urea transporters. We conclude that the impaired urinary concentrating ability associated with primary POLY in rats is due to impaired osmotic equilibration in the collecting duct that is mediated primarily by decreased AQP-2 protein abundance. Primary polydipsia, also known as psychogenic polydipsia or compulsive water drinking, is a frequent disord...
(POLY, n = 10; CTL, n = 10) were then killed by decapitation to avoid any influence of anesthesia on plasma AVP concentration. Trunk blood was collected for plasma AVP concentration, serum osmolality, serum sodium concentration, and serum creatinine concentration. In 12 rats (POLY, n = 6; CTL, n = 6) following decapitation, kidneys were rapidly removed and placed in chilled isolation solution. Kidneys were dissected on ice into cortex, outer medulla, and inner medulla regions for protein homogenization for subsequent Western blotting. One inner medulla from each rat was weighed and used for measurement of medullary osmolality. In eight rats (POLY, n = 4; CTL, n = 4), one inner medulla was prepared for V2 receptor studies.

**Evaluation of urinary concentrating ability, renal AQP water channels, sodium and urea transporters, and vasopressin V2 receptor mRNA following water deprivation in primary polydipsia.** After the 10-day treatment period, half of the animals (POLY, n = 10; CTL, n = 10) were subjected to a 36-h period of water deprivation, during which time food intake and urinary output were recorded. Urine was collected under oil, and urinary volume was measured every 12 h. In the final 6 h of the water deprivation period, urine was also collected for osmolality and creatinine. Animals were then killed by decapitation. Blood and tissue were processed as described above.

**Protein isolation.** After decapitation, kidneys were placed in ice-cold isolation solution containing 250 mM sucrose, 25 mM imidazole, 1 mM EDTA, pH 7.2, with 0.1% vol protease inhibitors (0.7 μg/ml peptatin, 0.5 μg/ml leupeptin, 1 μg/ml aprotinin) and 200 μM phenylmethylsulfonyl fluoride. Kidneys were dissected on ice into cortex, outer medulla, and inner medulla regions. Tissue samples were immediately homogenized in a glass homogenizer at 4°C. After homogenization, the protein concentration was determined for each sample by the Bradford method (Bio-Rad, Richmond, CA). Western blot analysis. Western blot analysis was performed to examine kidney expression of renal cortex AQP-1 and sodium-hydrogen antiporter (NHE3), outer medulla sodium-potassium-2 chloride (Na-K-2Cl) cotransporter and sodium-potassium-ATPase (Na-K-ATPase), and inner medulla urea transporter A1 (UTA1), AQP-2, AQP-3, and AQP-4. SDS-PAGE was performed on 8% acrylamide gels for Na-K-2Cl, NHE3, Na-K-ATPase, and UTA1, and on 12% acrylamide gels for AQPs. After transfer by electroelution to polyvinylidene difluoride membrane (Millipore, Bedford, MA), blots were blocked overnight with 5% nonfat dry milk in PBS (pH 7.4) with 0.1% Tween 20 (J. T. Baker, Phillipsburg, NJ), and the membranes were exposed to secondary antibody for 1.5 h at room temperature. Subsequent detection of the specific proteins was carried out by enhanced chemiluminescence (Amersham, Arlington Heights, IL) according to the manufacturer’s instructions. Prestained protein markers were used for molecular mass determinations. Densitometric results were reported as integrated values (area x density of band) and expressed as a percentage compared with the mean value in controls (100%). Membranes were stained with Coomassie blue to ensure equal loading.

**Antibodies.** Antibodies to AQP-2 (22) and to AQP-3, AQP-4, Na-K-2Cl, NHE3, and UTA1 (3, 6, 7, 21) have been previously characterized. Anti-Na-K-ATPase α-1 antibody was obtained from Upstate Biotechnology (Lake Placid, NY). Anti-AQP-1 antibody was obtained from Chemicon International (Temecula, CA).

**Differential centrifugation for AQP-2 trafficking.** Differential centrifugation was performed on inner medullary homogenates as previously described (6, 17). Inner medullary homogenates were initially centrifuged at 17,000 g for 20 min at 4°C to remove incompletely homogenized fragments and nuclei. The supernatant was saved. The pellets were resuspended in ice-cold isolation solution with protease inhibitors, homogenized on ice twice for 15 s each, and then centrifuged again at 17,000 g for 20 min at 4°C. The pellets (plasma membrane-enriched fraction) were retained, and the supernatants were combined and pelleted by centrifugation at 200,000 g for 60 min at 4°C (intracellular vesicle-enriched fraction). Protein measurement, sample preparation, and Western blotting for AQP-2 were performed as described above.

**Quantitative real-time RT-PCR.** RNA was isolated from inner medulla tissue using the Dneasy Tissue Kit (Qiagen, Valencia, CA) as per the manufacturer’s instructions. cDNA was prepared using the SuperScript First-Strand Synthesis System for RT-PCR kit (Invitrogen, Carlsbad, CA). The resulting cDNA was diluted 10-fold in sterile water, and aliquots were subjected to quantitative real-time RT-PCR. PCR primer pairs were designed using Primer Express 1.0 software (Applied Biosystems, Foster City, CA). The forward primer used was 5′-ATCCTTGTGCTCAGCTGATGTGGG-GAA-946, and the reverse primer used was 5′GCAATC-CAGGTCACATAGGCAC/GA-1022. A Smart Cycler (Cepheid, Sunnyvale, CA) was used. For normalization of samples, the dual-label probe assay for 18s RNA (VIC/TAMRA, Applied Biosystems) and the TaqMan PCR Core Reagent Kit (Applied Biosystems) were used. Nine-hundred nanomoles of forward and reverse primers were used together with 200 nmol of fluorescent probe. All experimental analyses were performed in triplicate. The relative amounts of experimental gene mRNA and 18s RNA PCR products were determined by comparison to a standard curve generated by serial dilution of a sample containing high levels of the target amplicons that were also run in triplicate. An arbitrary value of template was assigned to the highest standard and corresponding values to the subsequent dilutions. These relative values were plotted against the threshold value for each dilution to generate a standard curve. The relative amount for each experimental triplicate and 18s RNA triplicate was assigned an arbitrary value based on the slope and y-intercept of the standard curve. The average of 200,000 g centrifugal triplicates was divided by the average of the 18s RNA triplicate and the resulting normalized value (normalized copy ratio) was used for statistical analysis.

**Biochemical analyses.** Plasma AVP concentration was assessed by radioimmunoassay as described previously (11). Serum and urinary osmolality were measured by freezing-point depression (Advanced Instruments, Norwood, MA). Osmolar clearance was calculated as 24-h urinary volume x urinary osmolality/urinary osmolality. Solute-free water excretion was calculated as urinary flow rate – osmolar clearance. Serum and urinary creatinine were measured (Beckman Instruments). Twenty-four-hour creatinine clearances were used as an estimate of glomerular filtration rate. Serum sodium and potassium concentrations were measured by flame photometry.

**Medullary tonicity.** Each inner medulla sample was placed in a preweighed Eppendorf tube containing 250 μl of deionized distilled water. The tissue was homogenized in a glass homogenizer at 4°C. Tissue osmolality was measured by freezing-point depression (Advanced Instruments). The original tissue osmolality was estimated based on the nominal dilution factor and the assumption that 80% of the wet weight was water based on the method of Apostol et al. (1).
Statistical methods. The statistical analysis of results was performed using unpaired Student’s t-tests. Results were expressed as means ± SE with P < 0.05 considered significant.

RESULTS

Characteristics of CTL and POLY rats after 10 days of fluid intake. Body weight at the initiation of the study was comparable between study groups (Table 1). Body weight at the end of the fluid intake period before water deprivation was also comparable between study groups; this was expected because both study groups received the same amount and type of food and thus the same caloric and protein intake. Water intake and urinary output were significantly increased in POLY rats compared with CTL. POLY rats demonstrated decreased serum osmolality and serum sodium concentration compared with CTL rats. Serum potassium concentration was comparable between groups. As expected, urinary osmolality was decreased in POLY rats compared with CTL rats. Plasma AVP concentration was comparable between groups. Although this did not reach significance (POLY 39 ± 4 vs. CTL 48 ± 2%, P = 0.06).

Effect of primary polydipsia on renal sodium and urea transporters, AQP water channels, and vasopressin V2 receptor mRNA. Western blot densitometric results were reported as integrated values (area × density of band) and expressed as a percentage compared with the mean value in controls (100%). No significant differences were seen between CTL and POLY rats in renal abundance of cortical AQP-1 [densitometry CTL 100 ± 10 vs. POLY 100 ± 9% CTL mean, P not significant (pNS)], cortical NHE3 (CTL 100 ± 20 vs. POLY 100 ± 11% CTL mean, pNS), outer medulla Na-K-2Cl (CTL 100 ± 10 vs. POLY 100 ± 7% CTL mean, pNS), outer medulla Na-K-ATPase (CTL 100 ± 9% CTL mean, pNS), or inner medulla V2 receptor mRNA as assessed by RT-PCR was similar in CTL and POLY rats before any water deprivation.

Table 1. Characteristics of CTL and POLY rats after 10 days of fluid intake

<table>
<thead>
<tr>
<th></th>
<th>CTL</th>
<th>POLY</th>
<th>P</th>
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<tbody>
<tr>
<td>Body weight, g</td>
<td>285 ± 10</td>
<td>285 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Water intake, ml/day</td>
<td>22 ± 2</td>
<td>100 ± 1</td>
<td>0.0001</td>
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<tr>
<td>Urine output, ml/day</td>
<td>11 ± 1</td>
<td>80 ± 1</td>
<td>0.0001</td>
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<tr>
<td>Serum osmolality, mosmol/kgH2O</td>
<td>293 ± 2</td>
<td>277 ± 7</td>
<td>0.04</td>
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<tr>
<td>Serum sodium, meq/l</td>
<td>144 ± 1</td>
<td>138 ± 1</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum potassium, meq/l</td>
<td>5.0 ± 0.1</td>
<td>5.2 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma AVP, pg/ml</td>
<td>1.74 ± 0.36</td>
<td>0.29 ± 0.09</td>
<td>0.04</td>
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<tr>
<td>Urine osmolality, mosmol/kgH2O</td>
<td>1.365 ± 188</td>
<td>159 ± 13</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>0.43 ± 0.02</td>
<td>0.41 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>24-H creatinine clearance, ml/min</td>
<td>1.43 ± 0.13</td>
<td>1.51 ± 0.20</td>
<td>NS</td>
</tr>
<tr>
<td>Osmolar clearance, ml/day</td>
<td>12 ± 1</td>
<td>10 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>CH3O, ml/h</td>
<td>0 ± 3</td>
<td>69 ± 2</td>
<td>0.0001</td>
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</table>

Values are means ± SE. CTL, control; POLY, polydipsia; CH3O, solute-free water clearance; NS, not significant.

Fig. 1. Before any water deprivation, primary polydipsia (POLY; n = 6) was associated with a significant decrease in inner medullary protein abundance of aquaporin (AQP-2) by Western blotting compared with controls (CTL; n = 6; A). Densitometric results were reported as integrated values (area × density of band) and expressed as a percentage compared with the mean value in controls (100%). B: normalized copy ratio of vasopressin V2 receptor mRNA as assessed by RT-PCR was similar in CTL and POLY rats before any water deprivation.

15 vs. POLY 100 ± 15% CTL mean, pNS), or inner medulla UTA1 (CTL 100 ± 14 vs. POLY 112 ± 36% CTL mean, pNS). There was, however, a marked decline in inner medulla protein abundance of AQP-2 in POLY rats compared with CTL rats (POLY 76 ± 2 vs. CTL 100 ± 7, P < 0.007; Fig. 1A). There was also a significant decrease in AQP-2 protein abundance in the plasma membrane-enriched fraction of inner medulla in POLY rats compared with CTL rats (POLY 62 ± 3 vs. CTL 100 ± 7% CTL mean, P < 0.008). No significant differences were seen in inner medulla AQP-3 (CTL 100 ± 10 vs. POLY 100 ± 7% CTL mean, pNS) or AQP-4 (CTL 100 ± 18 vs. POLY 100 ± 30% CTL mean, pNS) between the study groups. No significant difference was noted in the normalized copy ratio of V2 receptor mRNA as assessed by RT-PCR in CTL and POLY rats (Fig. 1B).
Effect of primary polydipsia on urinary concentrating ability. After the treatment period, POLY and CTL rats were water deprived for 36 h (Fig. 2). POLY rats demonstrated significant weight loss with 36-h water deprivation compared with CTL (Fig. 2A). This was accompanied by hemoconcentration with POLY rats demonstrating increased hematocrit (56 ± 3 vs. 48 ± 2%, P < 0.02) compared with CTL. Urinary volume during the final 12 h of water deprivation was greater in POLY vs. CTL rats (Fig. 2B). Maximal urinary concentrating capacity in response to 36-h water deprivation was impaired in POLY rats (Fig. 2C). Plasma AVP concentration, measured following 36-h water deprivation, was increased in POLY rats (Fig. 3A). No significant differences were noted in medullary osmolality between study groups (Fig. 3B).

Effect of water deprivation during primary polydipsia on renal sodium and urea transporters, AQP water channels, and vasopressin V₂ receptor mRNA. Densitometric results were reported as integrated values (area × density of band) and expressed as a percentage compared with the mean value in controls (100%). No significant differences were seen between CTL and POLY rats in renal abundance of cortical AQP-1 (densitometry CTL 100 ± 4 vs. POLY 93 ± 8% CTL mean, pNS), cortical NHE3 (CTL 100 ± 14 vs. POLY 97 ± 5% CTL mean, pNS), outer medulla Na-K-2Cl (CTL 100 ± 8 vs. POLY 94 ± 7% CTL mean, pNS), outer medulla Na-K-ATPase (CTL 100 ± 20 vs. POLY 83 ± 10% CTL mean, pNS), or inner medulla UTA1 (CTL 100 ± 6 vs. POLY 99 ± 14% CTL mean, pNS). There was a marked decline in inner medulla protein abundance of AQP-2 in POLY rats compared with CTL rats (POLY 65 ± 5 vs. 100 ± 7% CTL mean, P < 0.0007). Outer medulla AQP-2 protein abundance was markedly decreased in POLY rats (POLY 16 ± 4 vs. CTL 100 ± 12% CTL mean, P < 0.0007) compared with controls. No significant differences were seen in inner medulla AQP-3 (CTL 100 ± 12 vs. POLY 83 ± 7% CTL mean, pNS) or AQP-4 (CTL 100 ± 10 vs. POLY 88 ± 9% CTL mean, pNS) between the study groups. However, there was a decrease in outer medulla AQP-3 protein abun-
Primary polydipsia, also known as psychogenic polydipsia or compulsive water drinking, is an important clinical entity, affecting patients with severe psychiatric illness (2). The effect of chronic primary polydipsia to impair urinary concentrating ability in response to dehydration or vasopressin administration was documented several decades ago by de Wardener and Herzheimer (4). However, the molecular mechanisms responsible for this finding had not been elucidated. The purpose of this study was to define the alterations in AQP{s and sodium and urea transporters that account for altered urinary concentration in rats with primary polydipsia.

We developed a novel model of primary polydipsia in rats. In our study, rats were induced to drink excessive amounts of water by administration of their daily food allowance dissolved in 100 ml of water. CTL rats received their daily food allowance as the same formula as powdered chow with ad libitum tap water. Because impaired urinary concentration has been shown to be a chronic, rather than acute, adaptation to primary polydipsia (4), primary polydipsia was induced in our rats for a 10-day period. In this model, rats with polydipsia demonstrated significant increases in water intake and urinary output, similar to humans with primary polydipsia. Serum sodium concentration and osmolality were also significantly decreased compared with CTL. Because hypokalemia has been previously associated with nephrogenic diabetes insipidus (NDI) and decreased AQP-2 protein abundance (16), serum potassium concentrations was measured in our rats. Despite high urinary flow rates, rats with primary polydipsia demonstrated serum potassium concentrations no different than CTL rats. Finally, our model of primary polydipsia was also associated with a significant impairment in urinary concentrating ability in response to 36-h water deprivation despite significantly higher plasma AVP concentrations compared with CTL. The current model has several benefits over previously used models such as sucrose administration. With our model, equal solute and caloric intake between POLY and CTL rats was achieved. In addition, protein intake is comparable, an important feature, as the effect of altered protein intake to impair renal AQP-2 expression has been described previously (20).

With the use of this model, it was then possible to examine the molecular mechanisms that contribute to impaired urinary concentration in chronic primary polydipsia. Using Western blot techniques, we were unable to show any effect of chronic polydipsia on the abundance of transporters that mediate either countercurrent multiplication or urea equilibration. However, as expected, chronic primary polydipsia was associated with a decrease in inner medulla AQP-2 protein abundance in the setting of diminished plasma AVP concentrations. Moreover, the membrane fraction of inner medulla AQP-2 was also reduced in POLY compared with CTL rats. No differences in vasopressin \( V_2 \) receptor mRNA as assessed by RT-PCR could be detected. These findings suggest that diminished inner medulla AQP-2 abundance is the result of chronically decreased vasopressin secretion in the setting of chronic high volume intake.

To examine the effects of chronic primary polydipsia on urinary concentrating capacity, water deprivation studies were performed. In addition to plasma AVP, urinary concentration is largely dependent on three factors: 1) creation of the medullary osmotic gradient by countercurrent multiplication; 2) urea equilibration; and 3) osmotic equilibration across the collecting duct from tubular fluid to medullary interstitium. The accumulation of sodium chloride and urea in the medullary interstitium, thus creating the osmotic gradient, is essential for the production of urine that is hyperosmotic to plasma. In the present study, there was no evidence of impaired countercurrent multiplication in POLY rats (26 ± 1 vs. 100 ± 24% CTL mean, \( P < 0.04 \)) vs. CTL. No significant difference was noted in the normalized copy ratio of \( V_2 \) receptor mRNA as assessed by RT-PCR in CTL and POLY rats (Fig. 4B).

**DISCUSSION**

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chronic primary polydipsia. Medullary osmolalities were comparable between POLY and CTL animals with water deprivation, thus arguing against a "washout" of the osmotic gradient during chronic primary polydipsia (18).

Recent studies in knockout mice (14) and humans (12) showed that abnormalities in AQP-1, presumably secondary to a defect in the descending limb of Henle's loop, are associated with a urinary concentrating defect. In the present study, abundance of AQP-1 protein was, however, no different between the POLY and CTL rats. The Na-K-2Cl cotransporter pump in the thick ascending limb, which constitutes the "einzelleffekt" (single effect) for the countercurrent concentrating mechanism (13), was also not different between the CTL and POLY rats. The protein abundances of other critical factors for tubular sodium transport, namely Na-K-ATPase and NHE3, were also comparable in the CTL and POLY rats.

Recent studies supported a role for AQP-2 water channels in the apical membrane of principal cells of the collecting duct as a critical factor in the urinary concentrating mechanism (reviewed in Ref. 19). The acute and long-acting effects of AVP are known to be critical in the synthesis and trafficking of the AQP-2 water channels. Thus, even with an intact countercurrent concentrating mechanism creating comparable osmotic gradients in the CTL and POLY rats, impairment in osmotic equilibration could occur in the presence of diminished AQP-2 water channels. This was observed in the present study as AQP-2 protein abundance rose significantly in the POLY rats as urinary fluid deprivation, but the inner medullary AQP-2 protein abundance was still significantly below that observed in the CTL animals. As anticipated, there was also a marked decline in the membrane fraction of inner medulla AQP-2 in POLY rats compared with CTL. The basolateral water channels in the collecting duct, namely AQP-3 and AQP-4, are also critical for the passive reabsorption of water in the inner and outer medulla. No significant changes in inner medulla AQP-3 or AQP-4 protein abundance were evident in this model. However, a marked decrease in outer medulla AQP-3 was present.

The effect of chronic primary polydipsia to impair maximal urinary concentrating capacity was clearly independent of AVP, because the POLY rats demonstrated markedly elevated plasma AVP concentrations in response to water deprivation compared with CTL rats. Our findings indicate that chronic suppression of plasma vasopressin during primary polydipsia results in downregulation of AQP-2, particularly in response to water deprivation. We were unable to demonstrate any alterations in vasopressin V2 receptor mRNA concentrations between the two study groups.

It is particularly remarkable that a more striking decrease in protein abundance of AQP-2 in the membrane preparation occurred compared with whole inner medulla homogenate. This finding suggests that in addition to an overall decrease of inner medulla AQP-2 protein abundance in POLY rats, there is also diminished trafficking of AQP-2 to the apical membrane. In this regard, further studies are needed to examine the effect of chronic primary polydipsia on AQP-2 trafficking. Such studies would specifically investigate vasopressin V2 receptor binding and affinity, adenylate cyclase activity, cAMP production, and phosphorylation of AQP-2 in this condition.

Previous studies demonstrated marked decreases in renal AQP-2 in models of NDI due to hypokalemia (16) or lithium treatment (15). Lithium treatment has been associated with intact vasopressin V2 receptor binding but diminished V2 receptor density in LLC-PK1 cells and rats (9), as well as decreased stimulation of Gso protein and associated inhibition of adenylate cyclase activity in LLC-PK1 cells (8). These are presumably toxic effects of lithium administration, as the decline in AQP-2 is very significant, and it takes several weeks for NDI to resolve following discontinuation of lithium (15). Diminished AQP-2 protein abundance due to hypokalemia has also been postulated to occur via a reduction in the production of cAMP (16), although further study of these mechanisms is required. It is unclear from the present results why chronic primary polydipsia is associated with a more significant diminution in urinary osmolality but less marked reduction in AQP-2 protein abundance compared with lithium- or hypokalemia-induced NDI.

In summary, chronic primary polydipsia has been shown to impair maximal urinary concentrating capacity in the rat in the presence of increased plasma vasopressin concentration, normal medullary osmotic gradient as generated by the countercurrent concentrating mechanism, and intact urea transporters. The defect in osmotic water equilibration between the medullary interstitium and tubular fluid was, however, associated with impaired total protein abundance and plasma membrane-enriched fraction of the critical AQP-2 water channel in the collecting duct as well as decreased outer medullary AQP-3 protein abundance.

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DISCLOSURES

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REFERENCES


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