Antidiuretic action of oxytocin is associated with increased urinary excretion of aquaporin-2

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Abstract

Background. The antidiuretic effect of oxytocin in humans is controversial. Urinary excretion of aquaporin-2 (AQP2) can be used as an index of the action of vasopressin on the kidney. We investigated whether exogenous oxytocin affects urinary concentration and urinary AQP2 excretion in human beings.

Methods. Oxytocin was administered intravenously at a rate of 20 mU/min in 10 healthy volunteers, seven patients with central diabetes insipidus (CDI) and three patients with nephrogenic diabetes insipidus (NDI). On the next day, 2 μg of 1-desamino-8-D-arginine vasopressin (dDAVP) was injected subcutaneously. Two-hour urine was collected before and after the administration of oxytocin and dDAVP, and urinary AQP2 was measured semi-quantitatively by western analysis.

Results. Urine volume and free water clearance were decreased, and urine osmolality was increased by the administration of oxytocin or dDAVP in the normal volunteers and CDI patients. Urinary AQP2 excretion was increased by oxytocin infusion in the normal volunteers (from 34 ± 12 to 326 ± 120 densitometry unit (DU)/2 h) and in the CDI group (from 8 ± 2 to 227 ± 92 DU/2 h) (P < 0.05), but not in the NDI group. dDAVP also had a similar but more potent effect on the urinary excretion of AQP2 in the normal and CDI groups.

Conclusions. Oxytocin has an antidiuretic effect and increases the urinary excretion of AQP2 in humans whose urinary concentration mechanism is preserved. These results suggest that AQP2 might have a regulatory role in the antidiuretic action of oxytocin in humans.

Keywords: antidiuretic; human; oxytocin; urinary AQP2

Introduction

Oxytocin is a nine amino acid peptide hormone secreted from the posterior pituitary gland with a well-established involvement in the female reproductive function. Because of its structural similarity to vasopressin and its presence in the neurohypophysis of males, its role as a hormone in other physiological processes, especially in renal function, has been under investigation for years. In animal studies, the influence of oxytocin on renal function depends upon the species used, the dosage of the hormone, the degree of hydration and the metabolic status of the animal [1,2]. In human studies, despite conflicting data [3], the weight of evidence favours some intrinsic antidiuretic effect of oxytocin in humans [4]. Moreover, case reports of water intoxication complicating the infusion of oxytocin to pregnant women support the antidiuretic action of oxytocin in humans [5]. Brattleboro rats were shown to concentrate their urine to hypertonic levels upon severe dehydration, and the plasma levels of oxytocin increased ~6-fold under this condition [6]. Recently, it has been documented that oxytocin can function as an antidiuretic hormone at physiological plasma levels, and that the V2 receptor and renal aquaporin-2 (AQP2) may mediate the antidiuretic action of oxytocin in rats [7–9]. However, the mechanism of the antidiuretic action of oxytocin in humans remains to be clarified.

AQP2 is the arginine vasopressin (AVP)-regulated water channel that mediates water transport across
the apical membrane of the renal collecting duct [10]. In response to AVP, AQP2 is translocated from cytoplasmic vesicles to apical plasma membranes by shuttle trafficking, increases water permeability of the membrane [11], and is again redistributed into cytoplasmic vesicles after removing AVP stimulation. Previous studies have shown that AQP2 protein is measurable in the urine of human subjects by either radioimmunoassay or quantitative western analysis [12]. Although the exact mechanism of excretion is unknown, urinary AQP2 may represent the altered levels of AQP2 in the apical plasma membrane of the collecting duct [13]. It is now considered that the changes in the urinary excretion of AQP2 can be used as an index of the acute action of AVP on the kidney [12].

The purpose of the present study was to ascertain whether oxytocin can affect urinary concentration in humans and whether the vasopressin-sensitive water channel, AQP2, plays a role in the antidiuretic effect of oxytocin. To explore this hypothesis, indices of the urinary concentration and urinary excretion of AQP2 before and after the infusion of oxytocin were compared in normal volunteers, patients with central diabetes insipidus (CDI) and patients with nephrogenic diabetes insipidus (NDI).

Subjects and methods

Subjects and study procedures

The normal group consisted of 10 subjects (all males, age range 20–24 years) without a history of hypertension, cardiovascular disease, diabetes or renal disease. Seven patients with central diabetes insipidus (five males, two females, age range 22–40 years) and three patients with nephrogenic diabetes insipidus (all males, age range 20–29 years) were involved in this study and described as the CDI and NDI groups, respectively. Water deprivation test revealed that three of the seven CDI patients were complete type, and four of them were incomplete type. Three NDI patients were congenital, but genetic abnormality was not delineated. All subjects were prohibited to take alcohol, tobacco, tea, coffee or medications for at least 48 h before and during the study.

In the morning of the first study day, all the participants were allowed to take light meals and encouraged to drink water (120 ml hourly) throughout the study period to maintain a urine volume. The CDI and NDI patients were allowed to drink more water if they felt thirsty. After voiding, urine samples were collected for 2 h, and blood samples were drawn from the antecubital vein for basal data. After basal samples had been taken, oxytocin was infused at a rate of 20 μU/min (30 U of oxytocin in 500 ml of 5% dextrose water) into subjects in a supine position. Thirty minutes after the start of the infusion, voiding took place, a 2 h urine collection was then performed and blood samples were drawn. On the second day of the experiment, the same procedure was used as on the previous day. Two hours after 2 μg of 1-desamino-8-D-arginine vasopressin (dDAVP) was injected subcutaneously, bladders were emptied and 2 h urine collection and blood sampling were performed. Water deprivation was performed on the following day in only the normal group and the subjects were instructed to avoid all intake for 24 h. After the 24 h of water deprivation, 4 h urine samples were collected and blood samples were taken. Urine volume was measured and blood and urine samples were analysed for osmolality (Osmomat 030, Gonotec, Berlin, Germany), electrolytes and creatinine using standard automated techniques (System E4A, Beckman Coulter Inc., Fullerton, CA). The remaining urine samples were stored at −70°C until AQP2 assay.

Written informed consent was obtained from all participants before they were enrolled in the study.

Urine preparation

A 25 ml aliquot of the collected urine was spun at 4000 g for 15 min at 4°C to remove cells, nuclei and large fragments. This urine supernatant was then centrifuged at 200 000 g for 1 h at 4°C and the resultant pellet was suspended carefully with 50 μl of dilution buffer [0.3 M sucrose, 25 mM imidazole, 1 mM EDTA, 8.5 μM leupeptin, 1 mM phenylmethylsulfonyl fluoride, pH 7.2]. The samples were then stabilized by adding 20 μl of 5 M Laemmli sample buffer (SDS 3.75 g, glicerol 15 ml, 1 M Tris, pH 6.8 2.5 ml, bromophenol blue dab, ddH2O to 50 ml), heated to 60°C for 20 min, and stored at −20°C until required for analysis. Just before being loaded for electrophoresis, samples were warmed at 37°C. To determine the relative amount of urinary AQP2, we used a reference urine sample. Fresh morning urine from a healthy male volunteer who was not enrolled in this study was taken and prepared as described above.

Semi-quantitative immunoblotting

Samples from the same subject were loaded into individual lanes of the same gel and 0.75 mg of creatinine equivalent of reference urine sample was loaded into the last lane of each gel. Preliminary studies determined the ranges of urine AQP2 densities that showed linearity ($r^2 = 0.979$, $P < 0.01$), and the loading amount of urine sample was determined for every urine sample to ensure the resultant AQP2 band density was in the linear range for analysis (Figure 1). The samples were then electrophoresed in 12% polyacrylamide–SDS minigels using a Mini PROTEAN III electrophoresis unit (Bio-Rad, Hercules, CA). For immunoblotting, the proteins were transferred electrophoretically from gels to nitrocellulose membrane (Bio-Rad). After being blocked with 5% skim milk in PBS-T (80 mM Na2HPO4, 20 mM NaH2PO4, 100 mM NaCl, 0.1% Tween-20, pH 7.5) for 30 min, membranes were probed overnight at 4°C with a 1:1000 dilution of rabbit anti-human AQP2 antibody. The AQP2 antibody (LL358) was characterized previously and kindly donated by Professor Soren Nielsen (Department of Cell Biology, Institute of Anatomy, Aarhus University). Membranes were washed and incubated with goat anti-rabbit IgG conjugated to horseradish peroxidase (31458; Pierce, Rockford, IL) diluted to 1:3000. Antigen–antibody reactions were visualized by enhanced chemiluminescence (ECLTM RPN 2106; Amersham Pharmacia Biotech, Buckinghamshire, UK) before being exposed to X-ray film (Hyperfilm; Amersham Pharmacia Biotech).

The density of the 29 kDa band of AQP2 was measured by densitometry (GS-700 Imaging Densitometry, Bio-Rad) and quantified using computer software (Molecular Analyst...
1.5, Bio-Rad). To compare the relative amount of urine AQP2 excretion, the band densities of each blot were adjusted based on the reference band density. The total AQP2 excretion during 2 h was calculated according to

$$\text{Total AQP2 excretion} \ [\text{densitometry unit (DU)/2 h}] = \frac{\text{adjusted band density}}{\text{total creatinine of 2 h urine}} \times \text{Creatinine equivalent of loaded sample}$$

The results are expressed in DU/2 h.

Statistics

Values are expressed as means±SEM. Comparisons were made between stimulated data and the basal level, except in the NDI group, using the Wilcoxon signed rank test (Statview software; Abacus Concepts Inc., Berkeley, CA). A P-value of <0.05 was considered significant.

Results

Normal volunteers

Data after oxytocin infusion, dDAVP injection or water deprivation were compared with the basal data in each group except in the NDI group. Table 1 summarizes the changes in serum and urinary parameters in the normal group. In the normal group, serum electrolytes and osmolality were unchanged, compared with the basal level. Urine output was decreased, although not significantly, from 446±75 to 289±53 ml/2 h after oxytocin infusion. After the subcutaneous injection of dDAVP (2 μg), urine output decreased significantly to 92±75 ml/2 h (P < 0.05, Figure 2). Urine osmolality increased significantly from 223±25 to 427±63 mOsm/kg H₂O after oxytocin infusion (P < 0.05). dDAVP and water deprivation showed a similar, though more potent, effect on the urine osmolality of the subjects than oxytocin (Figure 2). The administration of oxytocin decreased free water clearance from 110±51 to -57±51 ml/2 h in the normal group (P < 0.05). dDAVP injection and water deprivation also decreased free water clearance (Figure 2). The urinary excretion rates of electrolytes and the osmolality were not influenced by the administration of oxytocin or dDAVP in the normal group, and osmolal clearance was unchanged after the infusion of oxytocin (Table 1). Fractional excretion of sodium was decreased significantly only after water deprivation.

We were able to measure urinary AQP2 excretion in eight of the 10 normal subjects. In one of the eight normal subjects, no AQP2 signal was detected in urine of the basal state (Figure 4B). In the normal group, oxytocin significantly increased urinary AQP2 excretion from 34±12 to 326±120 DU/2 h (P < 0.05), and dDAVP and water deprivation also significantly
Oxytocin increases urinary aquaporin-2 excretion

Table 1. Serum and urinary parameters in the normal volunteers

<table>
<thead>
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<th></th>
<th>Basal</th>
<th>Oxytocin</th>
<th>dDAVP</th>
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<tbody>
<tr>
<td>sNa (mEq/l)</td>
<td>137.8±1.2</td>
<td>137.8±1.5</td>
<td>137.4±1.6</td>
</tr>
<tr>
<td>sOsm (mOsm/kg H2O)</td>
<td>282.7±0.9</td>
<td>280.8±1.6</td>
<td>280.3±1.3</td>
</tr>
<tr>
<td>uNa ExR (mEq/2h)</td>
<td>26±5</td>
<td>28±5</td>
<td>25±4</td>
</tr>
<tr>
<td>uK ExR (mEq/2h)</td>
<td>9.7±4.8</td>
<td>5.2±1.7</td>
<td>5.6±0.9</td>
</tr>
<tr>
<td>uOsm ExR (mOsm/2h)</td>
<td>95±16</td>
<td>97±12</td>
<td>87±10</td>
</tr>
<tr>
<td>FENa (%)</td>
<td>1.6±0.2</td>
<td>1.4±0.2</td>
<td>1.4±0.2</td>
</tr>
<tr>
<td>COsm (ml/2h)</td>
<td>337±56</td>
<td>346±43</td>
<td>311±37</td>
</tr>
</tbody>
</table>

Basal = basal data; oxytocin = data during continuous infusion of oxytocin (20 mU/min); dDAVP = data after subcutaneous injection of dDAVP (2 µg); dehydration = data after 24 h abstinence from food; sNa = serum sodium concentration; sOsm = serum osmolality; uNa ExR = excretion rate of sodium; uK ExR = excretion rate of potassium; uOsm ExR = osmolar excretion rate; FENa = fractional excretion of sodium; COsm = osmolar clearance.

*P < 0.05, compared with the basal level, Wilcoxon signed rank test. Values are expressed as means ± SEM.

Table 2. Serum and urinary parameters in the diabetes insipidus patients

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Oxytocin</th>
<th>dDAVP</th>
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<tbody>
<tr>
<td>CDI group (n = 7)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>sNa (mEq/l)</td>
<td>143.4±1.4</td>
<td>141.1±1.5*</td>
<td>139.4±0.9*</td>
</tr>
<tr>
<td>sOsm (mOsm/kg H2O)</td>
<td>293.6±4.7</td>
<td>283.3±3.3*</td>
<td>288.3±4.6*</td>
</tr>
<tr>
<td>uNa ExR (mEq/2h)</td>
<td>16±3</td>
<td>16±2</td>
<td>11±3</td>
</tr>
<tr>
<td>uK ExR (mEq/2h)</td>
<td>8.1±0.8</td>
<td>8.0±2.5</td>
<td>7.4±1.9</td>
</tr>
<tr>
<td>uOsm ExR (mOsm/2h)</td>
<td>71±9</td>
<td>63±7</td>
<td>54±11</td>
</tr>
<tr>
<td>FENa (%)</td>
<td>1.4±0.5</td>
<td>1.4±0.5</td>
<td>0.8±0.2*</td>
</tr>
<tr>
<td>COsm (ml/2h)</td>
<td>240±29</td>
<td>222±25</td>
<td>186±39</td>
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NDI group (n = 3)

<table>
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<tr>
<th></th>
<th>Basal</th>
<th>Oxytocin</th>
<th>dDAVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>sNa (mEq/l)</td>
<td>141.7±1.2</td>
<td>140.0±1.5</td>
<td>142.3±1.9</td>
</tr>
<tr>
<td>sOsm (mOsm/kg H2O)</td>
<td>288.0±4.5</td>
<td>287.7±2.4</td>
<td>294.7±3.3</td>
</tr>
<tr>
<td>uNa ExR (mEq/2h)</td>
<td>10±4</td>
<td>9±3</td>
<td>9±7</td>
</tr>
<tr>
<td>uK ExR (mEq/2h)</td>
<td>2.2±0.2</td>
<td>3.1±0.6</td>
<td>1.7±0.5</td>
</tr>
<tr>
<td>uOsm ExR (mOsm/2h)</td>
<td>35±3</td>
<td>44±8</td>
<td>42±24</td>
</tr>
<tr>
<td>FENa (%)</td>
<td>1.5±0.5</td>
<td>1.3±0.6</td>
<td>1.3±0.6</td>
</tr>
<tr>
<td>COsm (ml/2h)</td>
<td>243±23</td>
<td>306±66</td>
<td>298±177</td>
</tr>
</tbody>
</table>

Basal = basal data; oxytocin = data during continuous infusion of oxytocin (20 mU/min); dDAVP = data after subcutaneous injection of dDAVP (2 µg); dehydration = data after 24 h abstinence from food; sNa = serum sodium concentration; sOsm = serum osmolality; uNa ExR = excretion rate of sodium; uK ExR = excretion rate of potassium; uOsm ExR = osmolar excretion rate; FENa = fractional excretion of sodium; COsm = osmolar clearance

*P < 0.05, compared with the basal level, Wilcoxon signed rank test. Values are expressed as means ± SEM.

Fig. 3. Effects of oxytocin and dDAVP on urine volume, urine osmolality and free water clearance in diabetes insipidus patients. Water intake was maintained constant (120 ml/h) during the study except during water deprivation. Urine samples were collected for 2 h during continuous infusion of oxytocin (20 mU/min), 2 h after the subcutaneous injection of 2 µg of dDAVP, and for 4 h after 24 h water deprivation. Urine volume and free water clearance were decreased, and urine osmolality was increased after the infusion of oxytocin. The figures represent the means ± SEM of the obtained values.

basically after oxytocin infusion or dDAVP injection (P < 0.05), but not in the NDI group. Oxytocin infusion produced a decrease in urine flow (from 702±160 to 223±82 ml/2 h, P < 0.05) in the CDI group in which secretion of AVP was impaired, but not in the NDI group. Similarly, after the subcutaneous injection of dDAVP, urine output decreased in the CDI group, but not in the NDI group (Figure 3). Urine osmolality increased significantly from 391±53 mOsm/kg H2O after oxytocin infusion in the CDI group (P < 0.05), but oxytocin did not influence the urine osmolality in the NDI group. Also, dDAVP showed a similar effect on the urine osmolality of the subjects (Figure 3). Free water clearance decreased from 462±143 to 0.8±73 ml/2 h after oxytocin infusion in the CDI group (P < 0.05), but not in the NDI group. dDAVP injection also decreased free water clearance only in the CDI group (Figure 3). The urinary excretion rate of electrolytes and osmolar excretion rate were not changed by the administration of oxytocin or dDAVP in the CDI and NDI groups, and osmolar clearance and fractional excretion of sodium were unchanged after the injection of oxytocin or dDAVP in both groups (Table 2). We could measure urinary

increased urinary AQP2 excretion to 616 ± 140 and 298 ± 68 DU/2 h, respectively (P < 0.05, Figure 4C).

Diabetes insipidus patients

The changes in serum and urinary parameters in the DI groups are summarized in Table 2. In the CDI group, serum sodium concentration and osmolality decreased

significantly after oxytocin infusion or dDAVP injection (P < 0.05), but not in the NDI group. Oxytocin infusion produced a decrease in urine flow (from 702±160 to 223±82 ml/2 h, P < 0.05) in the CDI group in which secretion of AVP was impaired, but not in the NDI group. Similarly, after the subcutaneous injection of dDAVP, urine output decreased in the CDI group, but not in the NDI group (Figure 3). Urine osmolality increased significantly from 391±53 mOsm/kg H2O after oxytocin infusion in the CDI group (P < 0.05), but oxytocin did not influence the urine osmolality in the NDI group. Also, dDAVP showed a similar effect on the urine osmolality of the subjects (Figure 3). Free water clearance decreased from 462±143 to 0.8±73 ml/2 h after oxytocin infusion in the CDI group (P < 0.05), but not in the NDI group. dDAVP injection also decreased free water clearance only in the CDI group (Figure 3). The urinary excretion rate of electrolytes and osmolar excretion rate were not changed by the administration of oxytocin or dDAVP in the CDI and NDI groups, and osmolar clearance and fractional excretion of sodium were unchanged after the injection of oxytocin or dDAVP in both groups (Table 2). We could measure urinary

increased urinary AQP2 excretion to 616 ± 140 and 298 ± 68 DU/2 h, respectively (P < 0.05, Figure 4C).
AQP2 excretion in six of the seven CDI patients and two of the three NDI subjects. In three of the six CDI patients, no AQP2 signal was detected in urine of the basal state (Figure 5B), and a faint AQP2 signal was detected in the other three CDI patients (Figure 5A). Urinary AQP2 excretion was significantly increased from 8±2 to 227±92 DU/2h after the administration of oxytocin and to 400±170 DU/2h after injecting dDAVP in the CDI group (P<0.05, Figure 5C). However, in the NDI group, urinary AQP2 excretion was unchanged after oxytocin infusion or dDAVP injection (Figure 5C).

Discussion

In view of the structural similarity between oxytocin and AVP, it is not surprising that oxytocin has an effect on urinary concentration. Although results from animal studies on the renal effects of oxytocin vary according to the species used, the dosage of the hormone, the degree of hydration and the metabolic status of the animal [1,2], it seems that oxytocin produces an antidiuretic effect at least when AVP is suppressed or congenitally absent [1]. In human studies, although there are also conflicting results [3], evidence favours the antidiuretic action of oxytocin [4].

The present study shows that oxytocin has an antidiuretic action similar to that of AVP in humans, which confirms the results of a previous study [4]. In the CDI group in whom endogenous AVP secretion is impaired, urine flow and free water clearance were decreased and urine osmolality was increased, without any changes in urinary excretion of electrolytes and osmolality after the infusion of oxytocin in all subjects, which clearly showed that oxytocin had an antidiuretic action in humans. Decreased serum sodium levels and osmolality also support the antidiuretic effect of oxytocin in the CDI group (Table 2). Although the decrease in urine output after oxytocin infusion in the normal group was not statistically significant, urine osmolality was increased and free water clearance was decreased without a significant change in the electrolyte excretion rate and osmolar clearance. These results mean that oxytocin exerted an influence on the renal water reabsorption, not on the renal electrolyte. The infusion rate of oxytocin (20 mU/min) was chosen because it was in the range that oxytocin antidiuresis was found (15–45 mU/min) and 70% of the total antidiuretic effect occurred at infusion rates of 20–30 mU/min [4]. Although we did not measure plasma concentrations of oxytocin, the steady-state plasma level of oxytocin in normal men and women was achieved by 30 min after starting oxytocin infusion and increased linearly and dose dependently to well above the physiological concentrations in human beings [14].
used in this study was sufficient to induce the antidiuretic effect.

Urinary excretion of AQP2 in humans has been proposed to be a potential marker of collecting duct responsiveness to AVP [12], and AQP2 excretion in the urine depends on vasopressin action on principal cells rather than being a reflection of AQP2 expression in the whole kidney [12,13]. It has been documented that AVP binds the V2 receptor on the basolateral membrane of principal cells and initiates a cascade of events that results in the insertion of AQP2, which enhances the water permeability of the collecting duct. In the present study, urinary AQP2 excretion was increased during antidiuresis in the normal and in the CDI group when induced by both dDAVP injection and water deprivation, which is consistent with the results of previous studies [12]. Although the magnitude of the increment was less than that of dDAVP, oxytocin also produced an increase in urinary AQP2 excretion in parallel with its antidiuretic action in normal volunteers and CDI patients, which was similar to that of dDAVP (Figures 4 and 5). In NDI patients, a large 29 kDa AQP2 band, which is different from those previously reported in NDI patients bearing V2 receptor or AQP2 mutations [12], is not altered by the administration of oxytocin (Figure 5). Because distribution and targeting of AQP2 mutants is dependent on the mutations, this band might represent a misfolded AQP2 mutant [15,16]. Further evaluation including mutation analysis of these patients will be needed for the explanation for this band. Regardless of the pathogenesis of NDI in these patients, urinary AQP2 excretion was not responsive to the administration of oxytocin and dDAVP in the NDI patients, unlike in normal and CDI patients. This is the first report showing that the antidiuretic action of oxytocin is associated with increased urinary AQP2 excretion, and these observations further suggest that oxytocin might produce antidiuresis by regulating AQP2 possibly via the V2 receptor in humans.

Recently, the possibility that the antidiuretic action of oxytocin is mediated via the V3 receptor has been reported in animal studies. Terashima et al. reported that the acute elevation of the plasma oxytocin level downregulates V2 receptor mRNA expression and upregulates AQP2 mRNA expression without affecting the plasma AVP level [9]. According to in vitro microperfusion studies from rat inner medullary collecting duct (IMCD), the hydromosotic action of oxytocin is mediated by the V3 receptor [7,8]. Furthermore, Pouzet et al. showed that the antidiuresis induced by infusion of oxytocin in DI rats was completely abolished by the administration of a specific V3 receptor antagonist [17], and Jeon et al. recently reported that unique translocation of the AQP2 protein in rat kidney induced by oxytocin was mediated by the V3 receptor [18]. These results strongly suggest that the antidiuretic action of oxytocin is mediated not by the oxytocin receptor but by the V2 receptor, and we presume that similar mechanisms may be operative in humans. Oxytocin has an affinity for the V2 receptor two orders of magnitude lower that that of dDAVP [19]. Because these studies and ours, except for Chou’s in vitro experiment [8], were performed under the condition that the effect of AVP was eliminated or a pharmacological dose of oxytocin was administrated, the relatively low affinity of oxytocin for the V2 receptor might be overcome. However, the plasma level of oxytocin does not rise in response to chronic water restriction [20]. The role of oxytocin in urinary concentration under physiological conditions is uncertain as yet, and further evaluation will be needed.

Some authors have reported that factors other than AVP may influence urinary AQP2 excretion in humans [21]. However, this does not seem to be the case in the present study, because the urinary excretion rate of sodium, FENa, osmolal clearance, creatinine clearance and systemic blood pressure (data not shown) were not altered by the administration of oxytocin.

In conclusion, this study confirmed that exogenously infused oxytocin produces antidiuresis in humans whose urinary concentrating mechanism is preserved and that its antidiuretic action is accompanied by an increase in urinary AQP2 excretion. These results suggest that the antidiuretic effect of oxytocin might be mediated by regulating AQP2 in the collecting duct in humans. However, the role of oxytocin in urinary concentration under physiological conditions remains to be clarified.

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Conflict of interest statement. None declared.

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