Sleep deprivation induces excess diuresis and natriuresis in healthy children

B. Mahler,1,2 K. Kamperis,2 M. Schroeder,1 J. Frøkiaer,3,4 J. C. Djurhuus,1 and S. Rittig2

1Institute of Clinical Medicine, 2Department of Pediatrics, 3Department of Clinical Physiology, and 4Water and Salt Research Center, Aarhus University, Aarhus University Hospital, Skejby, Aarhus N, Denmark

Submitted 25 May 2011; accepted in final form 13 October 2011

Mahler B, Kamperis K, Schroeder M, Frokiaer J, Djurhuus JC, Rittig S. Sleep deprivation induces excess diuresis and natriuresis in healthy children. Am J Physiol Renal Physiol 302: F236–F243, 2012.— Urine production is reduced at night, allowing undisturbed sleep. This study was undertaken to show the effect of sleep deprivation (SD) on urine production in healthy children. Special focus was on gender and children at an age where enuresis is still prominent. Twenty healthy children (10 girls) underwent two 24-h studies, randomly assigned to either sleep or SD on the first study night. Diet and fluid intake were standardized. Blood samples were drawn every 4 h during daytime and every 2 h at night. Urine was fractionally collected. Blood pressure and heart rate were noninvasively monitored. Blood was analyzed for plasma antidiuretic hormone (AVP), atrial natriuretic peptide (ANP), angiotensin II, aldosterone, and renin. Urine was analyzed for aquaporin-2 and PGE2. Successful SD was achieved in all participants with a minimum of 4 h 50 min, and full-night SD was obtained in 50% of the participants. During SD, both boys and girls produced markedly larger amounts of urine than during normal sleep (477 ± 145 vs. 291 ± 86 ml, P < 0.01). SD increased urinary excretion of sodium (0.17 ± 0.05 vs. 0.10 ± 0.03 mmol·kg⁻¹·h⁻¹) whereas solute-free water reabsorption remained unchanged. SD induced a significant fall in nighttime plasma AVP (P < 0.01), renin (P < 0.05), angiotensin II (P < 0.001), and aldosterone (P < 0.05) whereas plasma ANP levels remained unchanged (P = 0.807). Nighttime blood pressure and heart rate were significantly higher during SD (mean arterial pressure: 78.5 ± 8.0 vs. 74.7 ± 8.7 mmHg, P < 0.001). SD leads to natriuresis and excess diuresis in healthy children. The underlying mechanism could be a reduced nighttime dip in blood pressure and a decrease in renin-angiotensin-aldosterone system levels during sleep deprivation.

natriuretic peptide (ANP) also show circadian variations, and a decrease in sodium excretion during sleep is observed (16). Nocturnal polyuria has been related to increased blood pressure in children with enuresis (19) and adults with nocturia (13). In adults, nocturnal urine output is indeed sensitive to acute sleep deprivation, causing excessive nocturnal sodium excretion (15). The nocturnal rise in AVP and the circadian rhythm in free water excretion is not as pronounced in adults as in children. Children have a clear circadian rhythm in both sodium and free water excretion (22), and therefore it is of interest to investigate the effect of sleep deprivation on both nocturnal water and sodium regulation in healthy children. The urinary excretion of aquaporin-2 (AQP2) has previously been used as a marker of free water regulation (6), and the urinary excretion of PGE2 is thought to reflect renal prostaglandin production with an effect on both sodium channels, renal hemodynamics, and AVP-regulated water reabsorption (14).

This study was undertaken to investigate the possible modulating effect of sleep deprivation on nocturnal urine production. Special focus was placed on boys and girls at an age where enuresis is still prominent. We wanted to describe the changes in renal water and solute handling together with changes in water- and sodium-regulating hormones (AVP, ANP, and RAAS), the excretion of PGE2 and AQP2, and hemodynamic variables. The in-patient study design was compared with everyday life using children’s home recordings.

MATERIALS AND METHODS

The study protocol was approved by the regional Committee on Biomedical Research Ethics, and informed consent was obtained from all participants.

Study subjects. Twenty healthy volunteers were recruited through hospital staff members. Inclusion criteria were age 8–12 yr, Tanner pubertal stage 1 or 2, and a normal physical examination including blood pressure measurement. Height and weight were within 2 SD of normal growth (42). Subjects also had complete bladder emptying upon voiding (determined by postvoid ultrasound) and normal urine dip-stick analyses. There was no history of day or night urinary or fecal incontinence after the age of 4 yr and no known history of prior severe illnesses or use of any medications, drugs, alcohol, or tobacco.

Study design. The experimental procedure consisted of two 24-h in-patient studies under standardized conditions regarding sodium and water intake for comparison of diuresis, blood pressure, and hormone profiles. One 24-h study was used for registration of baseline values, and the other 24-h study was used for registration of values during sleep deprivation. The order of baseline and sleep deprivation studies was randomized.

Participants were admitted to the Department of Pediatrics on the morning of the study. An intravenous, heparinized catheter was inserted in a cubital vein for blood sampling. During the experimental period, diet and fluid intake was standardized as directed by a clinical dietician (sodium 3 mmol/kg body wt and water 30 ml/kg body wt divided into two-thirds before 1600 and the remaining one-third until bedtime). Meals were served at 0800, 1200, and 1800, and caffeinated
beverages and additional servings were not allowed. Activity was allowed between 0000 and 2100. From 2100, the children had to be in a supine position in bed in a dimly lit room, and physical activity, food, and fluid intake were not allowed. The children were supervised by an adult during the entire period. Sleep deprivation was achieved by an adult talking to the children, telling stories, listening to their stories, and giving them small tasks, e.g., word and memory games, putting pearls on a string, knitting, drawing, building with Lego blocks, etc. Sleep during daytime was not allowed. At 0700 on the study day, the experimental procedure began. Blood samples were drawn every 4 h until 1900, thereafter every 2 h. Participants were in bed, resting in a supine position at least 15 min before each blood sample, and during the night of baseline recordings care was taken not to disturb the children’s sleep. To prevent clotting, the catheter was flushed with 10 ml isotonic saline and 0.25 ml heparin (50 IE) was installed. Blood samples were transported on ice, centrifuged at +4°C, and stored at −20°C unless immediately analyzed. All blood samples were analyzed for creatinine, urea, and osmolality. Blood samples from 1100 and subsequent sampling time points were analyzed for plasma concentrations of AVP, ANP, RAAS hormones (renin, angiotensin II, and aldosterone).

Urine was collected at 4-h intervals during daytime, starting after bladder emptying at 0700. Nighttime urine collection started at 2100 until the end of the study at 0700. All voidings were spontaneous, except after each blood sampling and before bedtime where the participants were asked to empty their bladder. The urine volume was measured, and the concentration of sodium, potassium, creatinine, and urea as well as osmolality were determined. Aliquots were stored at −80°C for analysis of PGE2 and AQP2. Leupeptin (60 µl, 0.05 mg/ml) and NaAzid (100 µl, 100 mM) were added to each 3-ml aliquot of urine for AQP2 analyses before storage, a modification of the urine storage method recommended by the National Institutes of Health Uroprotein Committee.(39)

Blood pressure and heart rate were measured at 30-min intervals during daytime and every hour during the night (noninvasively ambulatory blood pressure monitor, model 90207, Spacelabs).

Home recordings of sleeping habits and nighttime diuresis were obtained from all children. During a weekend following the admission, 48-h fluid intake and micturition pattern (time and volume) were recorded. On the following 5 school days, nighttime diuresis was recorded. Bedtime and time of awakening were noted on all registration days. There were no restrictions regarding fluid or food intake, activity level, or hours of sleep during home recordings.

Biochemical determinations. Plasma and urine osmolalities were determined using the freezing-point depression method (Osmometer 3900, Advanced Instruments). Sodium, potassium, creatinine, and urea measurements were carried out at the Department of Clinical Biochemistry (Vitros 950 analyzer).

Antidiuretic hormone (AVP) was measured in plasma following extraction in Sep-Pak Plus C18 cartridges (Waters, Milford, MA) using a previously described RIA (9). The highly specific AVP antibody (AB3096; produced by Dr. P. Bie, Dept. of Physiology and Pharmacology, University of Southern Denmark) was incorporated in the assay (2) with a detection limit of 0.10 pg/ml. The interassay and intra-assay coefficients of variation were 10.6 and 7.7%, respectively.

Renin was measured in EDTA-plasma by a commercially available kit (DSL-25100, Active Coated-Tube IRMA, Diagnostic Systems Laboratories, Webster, TX) with a detection limit of 0.7 pg/ml. The interassay and intra-assay coefficients of variation were 2.64 and 1.63%, respectively.

Angiotensin II was measured in plasma following ethanol extraction using a previously described RIA with modifications (17). The antibody was a rabbit anti-angiotensin II antibody (G225; produced by Prof. J. Danser, Dept. of Pharmacology, Erasmus University Medical Centre, Rotterdam, The Netherlands). The interassay and intra-assay coefficients of variation were 13.2 and 12.9%, respectively, and the detection limit was 0.9 pg/ml.

Aldosterone was determined in EDTA-plasma using a commercially available RIA kit (DSL-8600, Active Aldosterone Coated-Tube RIA, Diagnostic Systems Laboratories). The interassay and intra-assay coefficients of variation were 9.8 and 4.5%, respectively, and the detection limit was 7.64 pg/ml.

ANP concentration was determined in plasma by a commercially available RIA kit from Euro-Diagnostica (Malmö, Sweden). The detection limit was 3.5 pg/ml. The interassay and intra-assay coefficients of variation were 11.6 and 8.6%, respectively. There was no cross-reactivity with other natriuretic peptides.

PGE2 was measured in urine using an enzyme immunoassay of PGE metabolites (514531, Cayman Chemical). In urine, PGE2 undergoes extended metabolism, and therefore the assay is based on conversion of PGE2 and its metabolites to a single stable metabolite that gives a reliable estimate of the actual PGE2 level. The detection limit was 2 pg/ml, and the interassay and intra-assay coefficients of variation were 15 and 10%, respectively.

AQP2 was directly measured in urine by RIA using a modification of a previous described method (29, 35, 38). The detection limit was 16 pg/ml urine. The AQP2 measurements were performed at the Water and Salt Research Center, Aarhus University Hospital, Skejby.

During a screening visit, postvoid residual volume was measured by ultrasound (BVI 2500+, Verathon, Bothell, WA). Urine dip-stick was performed using a Multistix 7 (Bayer Diagnostics).

Calculations. On the basis of urine and plasma measurements, excretions (E) and clearances (C) were calculated for electrolytes, creatinine, urea, and osmoles using standard formulas (E = U × V, C = U × V/P × Δt, where U is urinary concentration, V is urine volume, P is the arithmetic mean of the plasma concentrations during the period, and Δt is the duration of the period). Solute-free water reabsorption (T,H2O) was calculated using the formula T,H2O (ml/min) = osmolar clearance (Cosm) − urine flow (Uflow). The clearance of creatinine was used as estimate of glomerular filtration rate (GFR) after adjusting for body surface area. Fractional excretions (FE) were defined according to the formula FE (%) = (C/creatinine clearance) × 100.

Statistics. Results are presented as means ± SD. A paired Student’s t-test was used for comparison between baseline and sleep deprivation; Δ values (baseline − SD) were tested for effect of sex using Student’s t-test. Daytime and nighttime parameters were separated, and plasma hormones and electrolytes were tested for effect of sleep deprivation, sex, and time in a mixed-effect model (modified MANOVA for repeated measurements). If the criteria for this model could not be fulfilled, mean values from baseline and sleep deprivation were tested with a paired Student’s t-test at each sampling point separately. All analyses were performed using STATA 10.0 software. Statistical significance was defined by a P value <0.05.

RESULTS

Demographic data of the participants are shown in Table 1. One boy was excluded after the first admission due to non-compliance (refusal to collect urine during sleep deprivation). Sleep deprivation was achieved in all participants with a
minimum of 4 h 50 min postponement of time to sleep and a full-night sleep deprivation in 50% of participants (Table 2). Both boys and girls were submitted to comparable length of sleep deprivation (girls median 6.25 h; boys 6.2 h, P = 0.85).

**Standardization and validity of the design.** Successful standardization was achieved based on comparable levels in all parameters during daytime. There were equal daytime results in all urine output parameters (Table 3), plasma hormone levels, plasma sodium, and plasma osmolality (Fig. 2). The daytime blood pressures and heart rates were the same on both days (Table 4), even though some differences were observed at single time points (Fig. 3).

The bedtime and time for morning rouse at admission were comparable to the ones at home (bedtime 2110 ± 40 min, awake 0700 ± 35 min), and the nighttime diuresis at home was similar to the one observed during baseline night of the in-patient study (baseline: 291 ± 86 ml; home recording: 285 ± 78 ml, P = 0.79).

**Diuresis.** A diurnal rhythm in diuresis was observed during baseline conditions. The baseline day-to-night urine production ratio was 3.15 ± 1.33, and the baseline day-to-night urine osmolality ratio was 0.44 ± 0.08 (Fig. 1).

Sleep deprivation had a dramatic effect on night diuresis, with an average increase of 68%: urine volume (baseline: 291 ± 86 ml; sleep deprivation: 477 ± 145 ml, P < 0.01). Reciprocal changes were seen in nocturnal urine osmolality from 877 ± 122 to 691 ± 171 mosmol/kgH₂O, P < 0.01 (Fig. 1). TcH₂O remained unaffected by sleep deprivation (Table 3, Fig. 1).

The effect of sleep deprivation on nocturnal diuresis was similar in both boys and girls [baseline vs. sleep deprivation; night urine volume: boys 0.41 ± 0.07, girls 0.61 ± 0.11 ml·kg⁻¹·h⁻¹, effect of sex (Psex) = 0.17; urine osmolality: boys −132 ± 38, girls −234 ± 64 mosmol/kgH₂O, Psex = 0.19]. There was no difference between boys and girls in TcH₂O (boys 0.09 ± 0.14, girls 0.06 ± 0.14 ml·kg⁻¹·h⁻¹, Psex = 0.88).

**Renal solute handling.** The excretion of osmolytes displayed a diurnal rhythm under baseline conditions. During nighttime, a pronounced decrease in excretion of electrolytes but no changes in the excretion of urea were detected (Table 3).

Sleep deprivation caused a 30% higher osmole excretion and 31% higher osmolar clearance during sleep deprivation. Sodium regulation was highly affected by sleep deprivation with a pronounced increase in sodium excretion, clearance, and fractional excretion (Table 3, Fig. 1). No difference between boys and girls in sodium excretion was observed (ENa: boys 0.07 ± 0.02, girls 0.09 ± 0.02 mmol·kg⁻¹·h⁻¹, Psex = 0.39). Potassium excretion and clearance were also increased during the sleep deprivation night, whereas fractional excretion did not change significantly (Table 3). Urea excretion, clearance, and fractional excretion were unchanged during sleep deprivation (Table 3).

**AQP2 and PGE₂.** AQP2 excretion showed a circadian rhythm under baseline conditions with a significant nighttime decrease (Fig. 1). Sleep deprivation caused a significant increase in nighttime excretion of AQP2 (Table 3).

PGE₂ levels also displayed a circadian rhythm under baseline condition with a significant nighttime decrease (Fig. 1), and sleep deprivation resulted in a pronounced increase in nighttime excretion (Table 3).

### Table 2. Number of successfully sleep-deprived participants at each blood sampling point during the intervention night

<table>
<thead>
<tr>
<th></th>
<th>2100</th>
<th>2300</th>
<th>0100</th>
<th>0030</th>
<th>0500</th>
<th>0700</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/20 (100%)</td>
<td>20/20 (100%)</td>
<td>20/20 (100%)</td>
<td>18/20 (90%)</td>
<td>15/20 (75%)</td>
<td>10/20 (50%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Urine output parameters.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Sleep Deprivation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 h</td>
<td>Day</td>
</tr>
<tr>
<td>Uflow, ml·kg⁻¹·h⁻¹</td>
<td>1.74 ± 0.37</td>
<td>2.40 ± 0.64</td>
</tr>
<tr>
<td>Uosm, mosmol/kgH₂O</td>
<td>482 ± 92</td>
<td>386 ± 77</td>
</tr>
<tr>
<td>GFR, ml·min⁻¹·1.73 m⁻²</td>
<td>174 ± 43</td>
<td>185 ± 52</td>
</tr>
<tr>
<td>ENa, mmol·kg⁻¹·h⁻¹</td>
<td>0.12 ± 0.02</td>
<td>0.15 ± 0.04</td>
</tr>
<tr>
<td>ENa, mmol·kg⁻¹·h⁻¹</td>
<td>0.52 ± 0.11</td>
<td>0.61 ± 0.20</td>
</tr>
<tr>
<td>CNa, ml/min</td>
<td>0.32 ± 0.09</td>
<td>0.35 ± 0.12</td>
</tr>
<tr>
<td>Ck, ml/min</td>
<td>8.89 ± 1.61</td>
<td>11.81 ± 2.16</td>
</tr>
<tr>
<td>FCa, %</td>
<td>5.34 ± 1.75</td>
<td>6.89 ± 2.33</td>
</tr>
<tr>
<td>Cu, mmol·kg⁻¹·h⁻¹</td>
<td>0.37 ± 0.08</td>
<td>0.37 ± 0.07</td>
</tr>
<tr>
<td>CCl, ml/min</td>
<td>42.35 ± 6.54</td>
<td>45.15 ± 6.59</td>
</tr>
<tr>
<td>FENa, %</td>
<td>25.85 ± 6.68</td>
<td>26.20 ± 6.59</td>
</tr>
<tr>
<td>ENa, mmol·kg⁻¹·h⁻¹</td>
<td>0.82 ± 0.16</td>
<td>0.90 ± 0.17</td>
</tr>
<tr>
<td>CNa, ml/min</td>
<td>1.68 ± 0.31</td>
<td>1.84 ± 0.34</td>
</tr>
<tr>
<td>TcH₂O, ml/min</td>
<td>0.66 ± 0.26</td>
<td>0.44 ± 0.33</td>
</tr>
<tr>
<td>E-AQP2, pg·kg⁻¹·h⁻¹</td>
<td>487 ± 288</td>
<td>524 ± 315</td>
</tr>
<tr>
<td>E-PGE₂, pg·kg⁻¹·h⁻¹</td>
<td>214 ± 71</td>
<td>271 ± 87</td>
</tr>
</tbody>
</table>

Values are means ± SD. Uflow, urine excretion rate; Uosm, urine osmolality; GFR, glomerular filtration rate; ENa, sodium (Na) excretion; CNa, Na clearance; FEa, fractional K excretion; EK, K clearance; FEX, fractional K excretion; Eurea, urea clearance; FEurea, fractional urea excretion; Eosm, osmolar clearance; Cnaosm, osmolar clearance; TcH₂O, solute-free water reabsorption; E-AQP2, urinary excretion of aquaporin-2 (AQP2); E-PGE₂, urinary excretion of PGE₂. Differences between baseline and sleep deprivation were independent of sex for all parameters. Differences between baseline and sleep deprivation: *P < 0.05, †P < 0.01, ‡P < 0.001.
No difference between boys and girls in the sleep deprivation effect on AQP2 or PGE_2 excretion was observed (AQP2: boys 139 ± 389, girls 226 ± 332 pg·kg\(^{-1}·h^{-1}\), \(P_{\text{sex}} = 0.60\); PGE_2: boys 30 ± 67, girls 51 ± 73 pg·kg\(^{-1}·h^{-1}\), \(P_{\text{sex}} = 0.51\)).

**Measurements in plasma.** Under baseline conditions, a significant circadian rhythm with higher nighttime levels compared with daytime levels was found in plasma AVP (\(P < 0.001\), renin (\(P < 0.001\)), and angiotensin II (\(P < 0.001\)). Plasma aldosterone, as expected, showed an inverse rhythm with the nadir at 2300 and peak levels during early morning (\(P < 0.001\)). Plasma ANP displayed a slight but significant peak at 2300 and significantly lower average levels during the night (Fig. 3).

Sleep deprivation was followed by a significant suppression of plasma AVP and aldosterone throughout the entire night (Fig. 2). The normal nocturnal increase in plasma renin and angiotensin II was clearly suppressed by sleep deprivation during the first part of the night at 2300 and 0100 (Fig. 2). Analysis of the volunteers with a full night’s sleep deprivation showed suppressed plasma renin (\(P < 0.01\)) and plasma angiotensin II (\(P < 0.01\)) throughout the entire night. Plasma ANP peaked 2 h after bedtime independently of sleep deprivation.

Girls had a tendency toward higher baseline levels of renin, and angiotensin II was significantly higher than in the boys (nighttime baseline renin: boys 117 ± 37, girls 136 ± 41 pg·ml\(^{-1}\), \(P_{\text{sex}} = 0.08\); nighttime baseline angiotensin II: boys 71 ± 29, girls 107 ± 42 pg·ml\(^{-1}\), \(P_{\text{sex}} = 0.03\)). Differences between baseline and sleep deprivation were unaffected by sex (baseline – sleep deprivation renin: boys 5 ± 12, girls 8 ± 13 pg·ml\(^{-1}\), \(P = 0.27\), baseline – sleep deprivation angiotensin II: boys 3 ± 11, girls 8 ± 14 pg·ml\(^{-1}\), \(P = 0.09\)) (Fig. 2). Both AVP, ANP, and aldosterone baseline levels and the effect of sleep deprivation were similar in boys and girls (Fig. 2).

**Hemodynamics.** Estimated GFR expressed a circadian rhythm during baseline conditions with a nighttime decrease, and this was unchanged by sleep deprivation (Table 3).

Blood pressure and heart rate had a clear circadian rhythm with a steep decline already evident at bedtime and consistent throughout the entire night (Table 4). Sleep deprivation resulted in higher nighttime levels of blood pressure and heart rate (Table 4), an effect that was prominent especially during the first part of the night (Fig. 3).

The difference between baseline and sleep deprivation was independent of sex for mean arterial pressure (MAP; \(P = 0.44\)), heart rate (\(P = 0.20\)), systolic blood pressure (\(P = 0.74\)), diastolic blood pressure (\(P = 0.47\)), and GFR (\(P_{\text{sex}} = 0.71\)).

**DISCUSSION**

We found a substantial increase in diuresis during acute sleep deprivation in healthy children. Excess nocturnal natriuresis and osmotic diuresis are the results of sleep deprivation, possibly mediated through marked changes in sodium-regulating hormones, prostaglandins, and blood pressure. Sleep deprivation blunts the nighttime fall in blood pressure and suppresses the normal increase in sodium-retaining hormones (renin, angiotensin II, and aldosterone). Solute \(\text{T}_{2}\text{H}_{2}\text{O}\) is unaffected by sleep deprivation despite suppressed nighttime plasma AVP.

The physiology behind the effect of sleep on renal functions is of special interest in children because of the high prevalence of nocturnal enuresis due to nighttime polyuria (8). Children compared with adults have a pronounced circadian rhythm in both sodium- and water-regulating hormones (22, 33). The pathophysiology behind nocturnal polyuria has been related in particular to a lack of nocturnal increase in plasma AVP (33), while recently other parameters has been investigated such as sodium regulation (1), urea excretion (25), prostaglandins (16), and blood pressure regulation (13, 19). Acute sleep deprivation has previously been investigated in adults, demonstrating a pronounced increase in diuresis (11, 20). This study is the first to describe an increase in diuresis as an effect of acute sleep deprivation in children.

Sodium excretion is linked to blood pressure and extracellular volume control, and the major sodium-retaining hormone system is the RAAS (26). We find a higher blood pressure and heart rate during sleep deprivation concurrent with suppressed plasma levels of all sodium-retaining hormones. Blood pressure and heart rate returned to the level of the baseline night during the last hours of the sleep deprivation night, probably reflecting the fact that some of the children fell asleep during the sleep deprivation night. Nocturnal blood pressure is related to nocturnal sodium excretion in salt-sensitive hypertension patients (40). Furthermore, increased blood pressure on polyuria nights was found in an outpatient study of children with enuresis (19), indicating a significant role of hemodynamics in nocturnal urine excretion. The excess diuresis in this study could be an effect of elevated blood pressure levels during sleep deprivation. The increase in nocturnal blood pressure did not significantly affect GFR or the filtered sodium load. A higher nighttime GFR has previously been proposed as the mechanism behind nocturnal polyuria in enuresis (7). This was not the mechanism behind the increased natriuresis in this

### Table 4. Blood pressure and heart rate during the 2 admissions

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Sleep Deprivation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day</td>
<td>Night</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>82.0 ± 8.6</td>
<td>74.7 ± 8.7</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>82.0 ± 15.0</td>
<td>71.5 ± 12.5</td>
</tr>
<tr>
<td>Systolic, mmHg</td>
<td>111.8 ± 9.9</td>
<td>104.2 ± 10.2</td>
</tr>
<tr>
<td>Diastolic, mmHg</td>
<td>66.8 ± 9.2</td>
<td>57.8 ± 9.2</td>
</tr>
</tbody>
</table>

Values are means ± SD. MAP, mean arterial pressure; heart rate, systolic and diastolic blood pressure during night and day from the 2 admissions. Daytime, no significant differences: MAP, \(P = 0.062\); heart rate, \(P = 0.300\); systolic, \(P = 0.298\); diastolic, \(P = 0.057\). Nighttime: *\(P < 0.01, †P < 0.01, ‡P < 0.001\).
study, but we used creatinine clearance, which may be too inconsistent to reflect real GFR changes (41). Moreover, our findings of a pronounced increase in fractional excretion sug-

Fig. 1. Effect of sleep deprivation on urine output parameters. Values are means ± SE. Sleep deprivation (SD) caused an increase in diuresis and excretion of osmoles. U-osm, urine osmolality; AQP2, aquaporin-2. Excretion (E-Na) and fractional excretion (FE-Na) of sodium were significantly higher, whereas solute-free water reabsorption (T_{H2O}) was unchanged on SD nights. *P < 0.05, **P < 0.01, ***P < 0.001 difference between baseline and sleep deprivation night.

changes rather than a central effect of sleep (5). We find that nonsleep increases blood pressure and decreases RAAS hormone levels. The primary stimulus might be either hormones or blood pressure, or it might be a centrally regulated parameter such as sympathetic tone. The order of the changes cannot be answered by this study but clearly should be the focus for future studies.

Local changes in the renal environment can also affect the reabsorptive activity in the nephron. Prostaglandins are potent modulators of the renal concentration mechanism with an effect on sodium channels, renal hemodynamics, and attenuation of AVP-regulated water reabsorption (14). Urinary excre-
tion of PGE\textsubscript{2} is thought to be an indicator of renal prostaglandin activity (12). We found increased excretion of PGE\textsubscript{2} during sleep deprivation, and, since the natriuretic properties of PGE are well established, it seems possible that PGE\textsubscript{2} is at least partly responsible for the observed natriuresis (16).

We can conclude that the excessive amount of sodium excreted during sleep deprivation nights is associated with reduced levels of the RAAS and higher blood pressure and heart rate. Whether the changes in sodium excretion reflect blood pressure or RAAS changes, or changes in central regulation with an effect on both systems, remains to be elucidated.

In healthy children, an increase in plasma AVP and solute T\textsubscript{2}H\textsubscript{2}O during nighttime are important parts of the normal reduction in nocturnal urine volume (22, 33). We could not detect an effect of acute sleep deprivation on free water handling in the kidney although clearly a suppression of plasma AVP was observed. Changes in plasma osmolality are the main stimulus for AVP regulation (34), and throughout sleep deprivation plasma osmolality levels were clearly below baseline values (Fig. 2). This could thus account for the decrease in plasma AVP levels together with a suppressive effect of increased arterial blood pressure (10). The lower

![Diagram: Twenty-four-hour variation in the plasma (P) levels of antidiuretic hormone (AVP), renin, angiotensin II, aldosterone, atrial natriuretic peptide (ANP), osmolality, and sodium. No significant differences during daytime were observed, but a significant effect of sleep deprivation was seen compared with nighttime values. Nighttime statistic in mixed-effect model: P\textsubscript{time}, comparable development over time; P\textsubscript{sex}, effect of sex; P\textsubscript{sd}, effect of sleep deprivation. *P < 0.05 paired t-test from a single time point.](http://ajprenal.physiology.org/)
plasma osmolality levels observed are confirmed by lower plasma sodium levels and probably reflect the renal loss of sodium during sleep deprivation nights since no fluid intake was allowed during both nights. Furthermore, the effect of AVP on free water regulation is highly dependent on the delivery and tonicity of the renal tubular fluid (37), which may be altered due to changes in sodium regulation.

In the collecting duct, water permeability is increased by insertion of AVP-regulated water channel AQP2 in the luminal membrane of the principal cells (27). The urinary excretion of AQP2 reflects the expression of AQP2 in the rat kidney (31). In humans, water loading suppresses and thirst stimulates urinary AQP2 excretion, and several conditions with altered water metabolism drastically change AQP2 excretion (6). Urinary AQP2 excretion in this study was higher during sleep deprivation, pointing toward increased recruitment of AQP2 canals. The fact that such changes are not translated into increased tubular water reabsorption may again be due to altered fluid tonicity in the collecting duct.

ANP-related polyuria has been observed in obstructive sleep apnea (18), where intrathoracic pressure is increased and hypoxia is present. Despite several studies, ANP has never been related to the polyuria seen in enuresis (16, 32). It is thus not surprising that we do not find an effect of sleep deprivation on the regulation of this hormone.

Boys and girls reacted similarly to sleep deprivation, with no gender differences in urine regulation. This is different to findings in adults, where men excrete substantially more sodium than women (15). A possible explanation could be the low sex hormone levels in early puberty, as sex hormones have an effect on both the RAAS as well as AVP (24, 36). In adults, no effect on free water regulation has been detected; on the contrary, we find lower levels of plasma AVP during sleep deprivation in children, as well as a decrease in plasma sodium levels and plasma osmolality. As opposed to adults, we also find significantly higher excretion of prostaglandins. Even though not all the children had a full night’s sleep deprivation, the effect was as pronounced as in adults with complete sleep deprivation and with a more pronounced effect on both free water regulation and prostaglandin production. If children produce more urine in response to sleep disturbances compared with adults, it could explain the higher incidence of polyuria-based enuresis in children.

The role of sleep and arousal in the pathology of enuresis has been subject to investigation since the 1960s but with no clear conclusion (3, 8, 28, 43). The increase in nocturnal diuresis observed in healthy children as a consequence of acute sleep deprivation is comparable to the nocturnal polyuria reported in a group of children with enuresis (16). Our findings elucidate the need for a reevaluation of sleep quality as part of the pathophysiology behind polyuria in enuresis. The close relationship between the regulation of the sleep-wake cycle, blood pressure, and nocturnal urine output points toward sleep induction or blood pressure-lowering treatment as possible new concepts in enuresis research and treatment.

Conclusion. This study is the first to demonstrate a significant increase in urine production during sleep deprivation in healthy children aged 8–12 yr. A blunting of the normal night dip in blood pressure and rise in RAAS hormones seems to be of importance whereas renal water handling seems unaffected. We found no sex differences in the effects of sleep deprivation. The study underscores the importance of sleep in the normal circadian regulation of urine output and points toward interesting new avenues of pharmacological modulation.
REFERENCES


AJP-Renal Physiol • doi:10.1152/ajprenal.00283.2011 • www.ajprenal.org

SLEEP AND NOCTURAL DIURESIS IN CHILDREN

F243

Downloaded from http://ajprenal.physiology.org, by 10.220.34.247 on July 7, 2017