Excess diuresis and natriuresis during acute sleep deprivation in healthy adults

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Kamperis K, Hagstroem S, Radvanska E, Rittig S, Djurhuus JC. Excess diuresis and natriuresis during acute sleep deprivation in healthy adults. Am J Physiol Renal Physiol 299: F404–F411, 2010. First published June 2, 2010; doi:10.1152/ajprenal.00126.2010.—The transition from wakefulness to sleep is associated with a pronounced decline in diuresis, a necessary physiological process that allows uninterrupted sleep. The aim of this study was to assess the effect of acute sleep deprivation (SD) on urine output and renal water, sodium, and solute handling in healthy young volunteers. Twenty young adults (10 male) were recruited for two 24-h studies under standardized dietary conditions. During one of the two admissions, subjects were deprived of sleep. Urine output, electrolyte excretions, and osmolar excretions were calculated. Activated renin, angiotensin II, aldosterone, arginine vasopressin, and atrial natriuretic peptide were measured in plasma, whereas prostaglandin E2 and melatonin were measured in urine. SD markedly increased the diuresis and led to excess renal sodium excretion. The effect was more pronounced in men who shared significantly higher diuresis levels during SD compared with women. Renal water handling and arginine vasopressin levels remained unaltered during SD, but the circadian rhythm of the hormones of the renin-angiotensin-aldosterone system was significantly affected. Urinary melatonin and prostaglandin E2 excretion levels were comparable between SD and baseline night. Hemodynamic changes were characterized by the attenuation of nocturnal blood pressure dipping and an increase in creatinine clearance. Acute deprivation of sleep induces natriuresis and osmotic diuresis, leading to excess nocturnal urine production, especially in men. Hemodynamic changes during SD may, through renal and hormonal processes, be responsible for these observations. Sleep architecture disturbances should be considered in clinical settings with nocturnal polyuria such as enuresis in children and nocturia in adults.

SLEEP IS THE ESSENTIAL BEHAVIORAL state that covers approximately one-third of our lives. Urine production is reduced during sleep, a necessary physiological process that allows sleep to be continued uninterrupted. Failure to do so leads to excess nocturnal diuresis, a common finding in clinical settings such as enuresis in children and nocturia in the elderly (36, 46). The sleep-arousal cycle affects a number of physiological processes considered important for renal function and the production of urine. Blood pressure is reduced during sleep in normotensive humans (6). Lack of this nocturnal dipping in blood pressure is a common finding in hypertension (13). Acute sleep deprivation (SD) leads to increased sympathetatic activity (48) and higher blood pressure (31), heart rate (16), and catecholamine excretion (22). Circadian variations are to be found in arginine vasopressin (AVP) secretion in children (38), and the hormones of the renin-angiotensin-aldosterone system (RAAS), all-important modulators of urine production. Lower nocturnal AVP levels have been demonstrated in enuretics with excess nocturnal urine production (38) although the exact reasons for this blunted AVP rhythm remain unclear. Recent research indicates excess sodium and osmotic excretion in selected populations of enuretics with nocturnal polyuria, as well as adults with nocturia (23, 32). Furthermore, studies indicate sleep architecture disturbances in children with enuresis (14, 47) although the relationship with renal function was not addressed. It has been hypothesized that abnormalities in nocturnal urine production may be the result of sleep architecture disturbances, but we are still short of experimental data that would allow definite conclusions.

The aim of this study was to investigate the impact of acute SD on the nocturnal urine production in young adults and to evaluate renal water and solute handling in a sleep-deprived state. A secondary aim was to evaluate the possible role of gender on the renal response to acute SD.

MATERIALS AND METHODS

Study subjects. The study protocol was approved by the local regional committee on biomedical research ethics, and informed consent was obtained from all participants. The protocol conformed to the recommendations for good clinical practice (CPMP/ICH/135/95). Twenty healthy adults (10 women) aged 18–35 yr (mean age 25 ± 1.5 yr) were included in the study. Healthy controls were recruited through the personnel and their acquaintances of the Department of Pediatrics and Department of Urology, Aarhus University Hospital, Skejby. Inclusion criteria for the participants were as follows: no history of urinary incontinence, no clinical or laboratory signs suggestive of an underlying disease, a normal urorflowmetry with residual urine assessment, an unrewarding clinical examination, and normal urinalysis.

Study design. Participants were admitted at the Department of Urology for two 24-h circadian studies. The two 24-h periods were identical apart from the fact that, during one, sleep was not allowed. The sequence of the two 24-h admissions was randomized. At 0730 on the day of admission, venous access was established through a heparinized cannula in a cubital vein. Starting at 0800, blood samples (25 ml) were taken every 3 h during the entire experimental period. Participants were ambulatory during the daytime but were asked to remain seated for at least 10 min before blood sampling. A volume of 10 ml isotonic saline and 0.5 ml heparin (100 IE/ml) was injected subsequent to blood sampling to prevent catheter clotting. Care was taken not to wake the participants during blood sampling during the nights where sleep was allowed.

Urine was fractionally collected with 3-h intervals following spontaneous voiding. Participants were asked to empty their bladders just after blood sampling, at bedtime, and upon wakening in the morning.

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All other micturitions were at free will. Normal activity was allowed from 0800 to 2200; hereafter, participants were asked to retire to their beds. The exact bedtime for each participant was noted. During the stay in the hospital, both water and sodium intake were standardized to 30 ml/kg and 3 mmol/kg, respectively, supervised by a clinical dietician. Meals were served at 0815, 1200, and 1730. Fluid intake was distributed as follows: two-thirds before 1600 and the remaining one-third until bedtime.

The following determinations were performed in plasma: sodium, potassium, creatinine, urea, osmolality, AVP, atrial natriuretic peptide (ANP), angiotensin II (ANG II), aldosterone (ALDO), and activated renin, whereas urine was analyzed for: sodium, potassium, urea, creatinine, osmolality, AVP, prostaglandin E2 (PGE2), and melatonin.

Blood samples were immediately centrifuged at 4°C and stored at −20°C unless immediately analyzed.

Blood pressure was measured every hour for the entire experimental period by means of an ambulatory blood pressure monitor (model 90207; Spacelab). During the nights with SD, participants retired to their beds at bedtime, and lights were dimmed. Participants were not allowed to fall to sleep or be ambulatory unless for voiding. During SD, participants were supervised during the entire night. Voiding commenced at will during the night, and the urine from all voidings following bedtime as well as the first morning voiding were pooled and constituted nighttime urine. Participants were weighted before the initiation of blood sampling and following the termination of the experimental period.

**Biochemistry determinations.** Determination of plasma sodium, potassium, creatinine, and urea were carried out at the Department of Clinical Biochemistry on a Kodak Ektachem 700XRC analyzer. In urine, sodium and potassium concentrations were measured using flame photometry (Eppendorf FCM6341 and MFM6350). Plasma and urine osmolalities were measured by the freezing point depression method (Osmometer 3900; Advanced Instruments).

ANP was measured in plasma following extraction in Sep-pak C18 cartridges (Water Associates) by means of RIA as previously described (44) and using a rabbit ANP specific antibody showing no cross-reactivity with other natriuretic peptides (Eurodiagnostica, Malmö, Sweden). The limit of detection was 1.5 pg/ml, whereas the intra- and interassay coefficients of variation were, respectively, 10%

### Table 1. Demographic data of the participants

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>25.3 ± 1.5</td>
<td>24.2 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Body wt, kg</td>
<td>81.7 ± 2.2</td>
<td>68.7 ± 5.7</td>
<td>&lt;0.05</td>
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<tr>
<td>Height, cm</td>
<td>178.9 ± 2.1</td>
<td>170.9 ± 1.9</td>
<td>&lt;0.05</td>
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<tr>
<td>n</td>
<td>10</td>
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</table>

Values are means ± SE; n, no. of subjects. There were no significant differences regarding age, but men were higher and heavier compared with women. NS, not significant.

All other micturitions were at free will. Normal activity was allowed from 0800 to 2200; hereafter, participants were asked to retire to their beds. The exact bedtime for each participant was noted. During the stay in the hospital, both water and sodium intake were standardized to 30 ml/kg and 3 mmol/kg, respectively, supervised by a clinical dietician. Meals were served at 0815, 1200, and 1730. Fluid intake was distributed as follows: two-thirds before 1600 and the remaining one-third until bedtime.

The following determinations were performed in plasma: sodium, potassium, creatinine, urea, osmolality, AVP, atrial natriuretic peptide (ANP), angiotensin II (ANG II), aldosterone (ALDO), and activated renin, whereas urine was analyzed for: sodium, potassium, urea, creatinine, osmolality, AVP, prostaglandin E2 (PGE2), and melatonin.
and 12%. ANG II was determined in plasma by RIA as previously described (24) with modifications, using a rabbit anti-ANG II antibody (Ab-5–03682; P. Christensen, Dept. of Clinical Physiology, Glostrup Hospital, Glostrup, Denmark). ANG II was extracted from plasma using Sep Pak C18 cartridges, methanol, and water. Intra- and interassay coefficients of variation were 9 and 13%, and the limit of detection was 1.4 pg/ml. A radioimmunoassay was used to determine ALDO in EDTA-plasma (Active Aldosterone Coated Tube RIA kit, Diagnostic Systems Laboratories, Webster, TX). The assay was performed with an intra-assay coefficient of variation of 7%, an interassay coefficient of variation of 13%, and a minimum detection limit of 25 pg/ml. Activated renin was directly measured in EDTA-plasma by a commercially available kit (Nichols Institute Diagnostics) using a monoclonal antibody against active renin showing 0.2% cross-reactivity with prorenin. Intra- and interassay coefficients of variation were 2 and 8%, and the detection limit was 1.4 μU/ml. Urine PGE2 concentration was measured by way of an enzyme immunoassay for metabolites (Cayman Chemical), which allowed us to reliably estimate the actual PGE2 levels in urine at the time of collection. To avoid bias due to the rapid PGE2 conversion to unstable metabolites, the assay is based on the conversion of PGE2 and its metabolic products to a single stable and measurable derivative (bicyclo-PGE2). Urine was diluted with a factor of 25 before analysis. Interassay and intra-assay coefficients of variation were ~15 and 10%. The detection limit was 2 pg/ml. AVP was directly measured in urine using a highly specific radioimmunoassay (Ab-5–030682; P. Christensen, Dept. of Clinical Physiology, Glostrup Hospital, Glostrup, Denmark). ANG II was extracted from body (Ab-5– 030682; P. Christensen, Dept. of Clinical Physiology, Glostrup Hospital, Glostrup, Denmark). ANG II was extracted from body (Ab-5–030682; P. Christensen, Dept. of Clinical Physiology, Glostrup Hospital, Glostrup, Denmark). ANG II was extracted from body (Ab-5–030682; P. Christensen, Dept. of Clinical Physiology, Glostrup Hospital, Glostrup, Denmark).

RESULTS

Table 1 shows demographic data of the participants. We compared urine output and urine osmolality during daytime between the two experimental periods to test the validity of the standardization protocol. We found no significant differences in diuresis, urine osmolality, sodium excretion, or total osmolic excretion during daytime, indicating acceptable repeatability in our experimental setup.

**Diuresis and urine osmolality.** During the baseline circadian study, significant variations in diuresis (Uflow) and osmolality were evident during the 24-h period as shown in Fig. 1 and Table 2. The observed reduction in Uflow (from 1.51 ± 0.12 to 1.0 ± 0.07 ml·kg⁻¹·h⁻¹, P < 0.01) was more pronounced in women (daytime 1.75 ± 0.17 ml·kg⁻¹·h⁻¹, night 0.98 ± 0.09 ml·kg⁻¹·h⁻¹) compared with men (daytime 1.27 ± 0.12 ml·kg⁻¹·h⁻¹, night 1.05 ± 0.10 ml·kg⁻¹·h⁻¹), mainly due to the fact that women shared higher diuresis values during daytime. Women showed a trend toward higher nocturnal urine osmolalities (467 ± 52 mosmol/kgH2O compared with 364 ± 30 mosmol/kgH2O, P = 0.11), but differences between genders did not reach statistical significance.

SD had a dramatic impact on urine output with a >50% increase in nocturnal diuresis (from 1.01 ± 0.06 to 1.61 ± 0.13 ml·kg⁻¹·h⁻¹, P < 0.001), and a reduction in osmolality (from 416 ± 32 to 366 ± 15 mosmol/kgH2O, P < 0.001). Men reached higher nocturnal diuresis values during SD compared with women (1.82 ± 0.22 compared with 1.41 ± 0.11 ml·kg⁻¹·h⁻¹). Reflecting these observations, we found a significant gender-SD interaction (P < 0.01).

Solute-free water reabsorption was not influenced by SD (Fig. 1), since the observed T₃H₂O levels were not significantly different between baseline night and SD night.

Table 2. Baseline day and night values as well as values during SD for the different parameters in men and women

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men</th>
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<th>Women</th>
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<tr>
<td></td>
<td>Day</td>
<td>Night</td>
<td>SD</td>
<td>Day</td>
<td>Night</td>
<td>SD</td>
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<tr>
<td>Uflow, ml·kg⁻¹·h⁻¹</td>
<td>1.27 ± 0.12</td>
<td>1.05 ± 0.10</td>
<td>1.82 ± 0.22</td>
<td>1.75 ± 0.17</td>
<td>0.98 ± 0.09</td>
<td>1.40 ± 0.11</td>
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<tr>
<td>Uosmol, mosmol/kgH₂O</td>
<td>464 ± 69</td>
<td>364 ± 30</td>
<td>359 ± 25</td>
<td>362 ± 30</td>
<td>467 ± 52</td>
<td>373 ± 16</td>
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<tr>
<td>GFR, ml/min</td>
<td>147 ± 58</td>
<td>128 ± 12</td>
<td>140 ± 51</td>
<td>127 ± 9</td>
<td>120 ± 6</td>
<td>120 ± 6</td>
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<tr>
<td>Eosmol, mosmol/kgH₂O</td>
<td>0.073 ± 0.007</td>
<td>0.051 ± 0.003</td>
<td>0.135 ± 0.103</td>
<td>0.088 ± 0.011</td>
<td>0.076 ± 0.006</td>
<td>0.112 ± 0.011</td>
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<td>FEK, %</td>
<td>0.04 ± 0.05</td>
<td>0.04 ± 0.03</td>
<td>0.09 ± 0.09</td>
<td>0.059 ± 0.06</td>
<td>0.046 ± 0.06</td>
<td>0.07 ± 0.10</td>
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<tr>
<td>FEK, %</td>
<td>0.063 ± 0.005</td>
<td>0.034 ± 0.002</td>
<td>0.061 ± 0.008</td>
<td>0.077 ± 0.007</td>
<td>0.041 ± 0.006</td>
<td>0.040 ± 0.003</td>
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<tr>
<td>FEK, %</td>
<td>13.06 ± 1.46</td>
<td>8.90 ± 0.75</td>
<td>14.35 ± 1.80</td>
<td>17.33 ± 2.51</td>
<td>9.43 ± 1.54</td>
<td>10.24 ± 0.77</td>
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<tr>
<td>Eosmol, mosmol/kgH₂O</td>
<td>0.25 ± 0.01</td>
<td>0.16 ± 0.07</td>
<td>0.20 ± 0.01</td>
<td>0.23 ± 0.02</td>
<td>0.17 ± 0.02</td>
<td>0.17 ± 0.01</td>
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<tr>
<td>FEK, %</td>
<td>44.44 ± 3.68</td>
<td>42.37 ± 1.49</td>
<td>48.67 ± 2.01</td>
<td>51.71 ± 2.87</td>
<td>42.71 ± 3.03</td>
<td>48.01 ± 2.76</td>
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<tr>
<td>Eosmol, mosmol/kgH₂O</td>
<td>0.53 ± 0.04</td>
<td>0.36 ± 0.02</td>
<td>0.61 ± 0.04</td>
<td>0.60 ± 0.04</td>
<td>0.42 ± 0.03</td>
<td>0.51 ± 0.02</td>
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<tr>
<td>T₃H₂O, ml/min</td>
<td>0.81 ± 0.27</td>
<td>0.52 ± 0.12</td>
<td>0.48 ± 0.13</td>
<td>0.42 ± 0.16</td>
<td>0.57 ± 0.09</td>
<td>0.47 ± 0.05</td>
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<tr>
<td>AVP, ng·kg⁻¹·h⁻¹</td>
<td>0.100 ± 0.010</td>
<td>0.080 ± 0.009</td>
<td>0.088 ± 0.003</td>
<td>0.127 ± 0.046</td>
<td>0.069 ± 0.027</td>
<td>0.078 ± 0.005</td>
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<tr>
<td>FEAVP, ng·kg⁻¹·h⁻¹</td>
<td>0.38 ± 0.07</td>
<td>0.35 ± 0.06</td>
<td>0.39 ± 0.09</td>
<td>0.19 ± 0.01</td>
<td>0.16 ± 0.02</td>
<td>0.23 ± 0.03</td>
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<tr>
<td>MAP, mmHg</td>
<td>90.4 ± 2.2</td>
<td>81.6 ± 2.8</td>
<td>85.3 ± 1.3</td>
<td>84.2 ± 1.3</td>
<td>74.1 ± 1.9</td>
<td>82.3 ± 2.2</td>
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</table>

Values are means ± SE. SD, sleep deprivation; Uflow, diuresis; Uosmol, osmotic urea; GFR, glomerular filtration rate; FEK, %, fractional excretion of sodium, potassium, and urea, respectively; Eosmol, excretion of urea; Eosmol, osmotic excretion; T₃H₂O, solute free water absorption; FEAVP and FEK, %, excretion of arginine vasopressin and prostaglandin E₂, respectively; MAP, mean arterial pressure. Baseline vs. SD: *P < 0.05 and †P < 0.01. Gender-SD interaction: ‡P < 0.05 and §P < 0.01.
**Solute excretion.** Under normal conditions, the urinary osmolar excretion follows a diurnal rhythm with significant reductions during sleep as shown in Fig. 1. Acute SD blunted this rhythm, and osmotic clearance was significantly increased during SD nights, approximating levels seen during daytime. The effect was more pronounced in men (0.36 ± 0.02 to 0.61 ± 0.04 mosm·kg⁻¹·h⁻¹) than women (0.42 ± 0.02 to 0.51 ± 0.02 mosm·kg⁻¹·h⁻¹, *P* < 0.05 for gender-SD interaction). Comparable results were seen for Cosm.

Acute SD led to excess natriuresis, and the effect was clearly more pronounced in men (0.051 ± 0.003 to 0.135 ± 0.013 mmol·kg⁻¹·h⁻¹) than women (0.067 ± 0.006 to 0.112 ± 0.011 mmol·kg⁻¹·h⁻¹, *P* < 0.001, for the effect of SD and *P* < 0.05 for the gender-SD interaction). Similar effects could be demonstrated for both clearance and fractional excretion of sodium (Fig. 2 and Table 2).

The normal diurnal rhythm of potassium excretion, evident during baseline, was altered by SD, with subjects showing increased nocturnal potassium excretion, clearance, and fractional excretion compared with baseline (Fig. 2). The impact was again more pronounced in men compared with women (*P* < 0.05 for gender-SD interaction).

Significant differences were also seen in the effect of SD on renal urea handling between sexes. In women, excretion of urea remained unchanged during SD, but in men excretion of urea was significantly higher in the sleep-deprived state (Fig. 2).

SD seems to alter the GFR as this was evaluated by creatinine clearance. The overall increase in GFR during SD was primarily seen in men while in women we found no significant effect of SD on GFR (Table 2). There was a significant gender-SD interaction (*P* < 0.05).

**Plasma hormone profiles.** A graphical synopsis of the impact of SD on the measured hormones can be seen in Fig. 3. The circadian variation in ANP levels was evident and remained unchanged during SD. Both activated renin and ANG II were significantly suppressed during SD, and the effect was similar in both sexes (gender-SD interaction *P* = 0.81 and *P* = 0.88, respectively). Similarly, SD reduced the nocturnal plasma ALDO levels, an effect that was seen in both genders (gender-SD interaction *P* = 0.88).

AVP levels in plasma did not seem to be influenced by SD in either men or women, although a trend toward higher AVP levels was evident during the last hours of the SD night. Urinary...
excretion of AVP was also similar between baseline and SD nights (Table 2).

Melatonin measured in urine expressed a clear circadian rhythm with almost a fourfold increase during the night (Table 2). Acute SD did not influence this variation, and the levels of the hormone were not different between baseline and SD nights.

The nocturnal levels of PGE2 measured in urine were not significantly affected by SD compared with the baseline night.

Fig. 3. Diurnal variations in plasma (p) levels of aldosterone (ALDO), renin, angiotensin II (ANG II), atrial natriuretic peptide (ANP), arginine vasopressin (AVP) as well as serum levels of sodium (s-Na) and osmolality (s-Osm) during baseline and SD. *P < 0.05, **P < 0.01, and ***P < 0.001.
Men shared significantly higher PGE$_2$ excretion levels compared with women (Table 2).

**Hemodynamics.** For the purpose of hemodynamic evaluation, the mean arterial pressure (MAP) and heart rate were analyzed. The well-described nighttime dip in MAP was evident during baseline night (Table 2 and Fig. 4). During SD, this dipping was largely attenuated, an observation made in both men and women. MAP levels during nights with SD, although higher compared with baseline nights, did not reach the levels seen during daytime. We found no gender-SD interaction for MAP changes. Diurnal variations were also evident in heart rate, with lower levels during the night. SD did not significantly influence HR. Figure 5 shows the relationship between night-to-day ratios in MAP and GFR and the night-to-day ratios in sodium excretion.

**DISCUSSION**

We herein describe that acute SD leads to excess urine production, an effect evident in both sexes although more pronounced in men. The amount of urine produced during these sleepless nights by far exceeds bladder reservoir ability, thus leading to nocturia. This is an important finding with possible pathophysiological implications in clinical and experimental settings. Enuresis in children and nocturia in elderly is in many cases the result of excess nocturnal urine production. Disturbances in the vasopressin-aquaporin (AQP) axis (38, 37) have long been considered as the basis of the nocturnal polyuria seen in enuresis. However, during recent years, factors outside of this axis have also been implicated. Abnormal renal sodium handling (1, 32), aberrations in the urinary osmotic excretion (29), and excess renal prostaglandin production (23) have all been associated with the nocturnal polyuria of enuresis. A recent study in enuresis has even indicated differences in blood pressure profiles during nights with excess diuresis (27). The nocturnal polyuria of the elderly seems even more complicated. Alterations in hemodynamics (33), AVP regulation (40), ANP secretion (12), the RAAS (45), and the autonomic system (35) have been described in the elderly. The present study indicates that sleep architecture may play an additional important role in this interplay of physiological processes that lead to excess nocturnal urine production.

Increased diuresis following prolonged SD has been described in early studies performed in humans (16, 28). The dramatic increase in diuresis in response to acute SD described herein seems not attributable to AVP-AQP2 axis changes. AVP profiles, and the renal solute free water handling, the end product of AVP-AQP2 axis activation, remained unchanged during SD. This becomes an interesting finding indicating that nocturnal polyuria may ensue independent of the renal water handling. Natriuresis is held responsible for the observed polyuria in chronic kidney disease, and this excess sodium excretion seems related to altered hemodynamics in these patients (17, 18). Observations in enuretics with desmopressin-resistant nocturnal polyuria suggest abnormal sodium excretion profiles and aberrations in renal sodium handling (23). The hypothesis exists that sleep architecture disturbances may somehow lead to natriuresis and excess nocturnal urine excretion.

Confirming this hypothesis, we demonstrate that acute SD acts on several systems that govern sodium homeostasis. The nocturnal levels of plasma renin, ANG II, and ALDO are suppressed during SD, directly leading to reduced sodium reabsorption in renal tubuli. The circadian rhythms of these hormones are well described (7, 9, 25). Our study is in accordance with previous studies showing that SD disturbs the normal 24-h variations in RAAS (10, 30). This suppression of the RAAS may be the result of a direct effect of SD on the sensitivity of the RAAS but could also be mediated through sympathetic-parasympathetic system disparities. We know that variations exist in renin levels during the different sleep stages, with suppressed levels during non-REM sleep (11), a sleep stage characterized by increased sympathetic activity (42). It can be thus hypothesized that SD, being a stressor factor, may increase sympathetic activity, thus resetting the RAAS regulation, with natriuresis as the net effect. The altered hemodynamics, evident in the present study, could also directly or indirectly lead to natriuresis. The clear increase of MAP is a clear effect of acute SD. This attenuation of the nocturnal
blood pressure dipping may represent the stimulus leading to corresponding changes in sodium-regulating hormones of the RAAS with natriuresis as part of the blood pressure autoregulation loop. It may also directly affect GFR, local renal hemodynamics, and sodium filtration fraction. Indeed, a slight but significant increase was seen in GFR during SD but mainly men. The significance of this modest GFR increase for the nocturnal diuresis is questionable. Studies on children with enuresis (27) and studies in elderly men with nocturia (20) associate the nocturnal polyuria observed with increased nocturnal BP profiles. It can therefore be hypothesized that sleep quality disturbances may be the common denominator for these observations.

ANP is another major modulator of sodium excretion with a clear circadian rhythm (15) but does not seem to mediate the SD-induced natriuresis. Nocturnal levels of the peptide were unaltered during SD, despite the attenuation of nocturnal blood pressure dipping. In clinical settings related to disturbed sleep due to sleep apnea, ANP plays a pivotal role in the observed natriuresis and polyuria (4), but a similar role is not supported by our findings during SD.

PGE2 is the most abundant renal prostanoid. It counteracts the renal tubular actions of AVP (2, 5) but also exerts direct natriuretic properties in the renal tubules (3, 8). Excess renal PGE2 excretion was demonstrated in children with enuresis and nocturnal polyuria (23), suggesting a role for this autacoid in polyuric states. A recent study in humans subjected to 3 days of SD show increased PGE2 excretion (21). In the present study, acute SD did not significantly alter PGE2 levels. It may be possible that the alterations in prostaglandin excretion profile become more evident during prolonged periods of SD. Whether prostaglandins represent a mediator of SD-related natriuresis needs further elucidation.

Melatonin, a solid circadian rhythm modulator, remains uninfluenced by acute SD, a finding supporting previous observations (19, 30), although data opposing these conclusions are also to be found in the literature (41). Melatonin does not seem to mediate these SD-related changes in renal sodium handling.

A consistent finding in this study was the differences between genders in the degree of the SD-induced diuresis and natriuresis. Men seem more vulnerable to SD, presenting with higher diuresis and natriuresis levels. Considering the higher incidence of enuresis, nocturia, but also hypertension in men, this becomes a particularly interesting finding. Differences exist in sodium homeostasis between genders. Women share lower BP and higher RAAS hormone levels (34, 43) although sodium excretion is comparable between sexes. Because the hemodynamic changes seen in the present study are more pronounced in men, this may be the reason why men share higher diuresis and natriuresis levels during SD. Differences between sexes with regard to renal sodium handling seem to exist on the molecular level as well. Kienitz et al. (26) find the epithelial sodium channel ENaC, an important site of renal tubular sodium regulation, to be upregulated by androgens and downregulated by estrogens. The more pronounced natriuresis in men as described in the present study may just reflect these differences in the renal sodium handling potentials between genders. The clinical importance of these male-female discrepancies in sodium regulation needs further elucidation.

The present study attempts an insight into the renal effects of acute SD in young healthy volunteers. Nights deprived of sleep are characterized by natriuresis, osmotic diuresis, and a dramatic urine output increase. Blood pressure dipping is attenuated, and the RAAS is clearly suppressed. It is of particular importance to evaluate sleep architecture and its disturbances in clinical settings with nocturnal polyuria and natriuresis such as enuresis in children and nocturia in the elderly.

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