Race, sex, and the regulation of urine osmolality: observations made during water deprivation

Michael L. Hancock 2nd,1,2 Daniel G. Bichet,3 George J. Eckert,2 Lise Bankir,4 Mary Anne Wagner,1,2 and J. Howard Pratt1,2
1The Richard L. Roudebush Veterans Affairs Medical Center and 2Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana; 3Departments of Medicine and Physiology, Université de Montréal, Hôpital du Sacré-Cœur de Montréal, Montréal, Québec, Canada; and 4INSERM Unit 872, Université Pierre et Marie Curie (Paris VI), Centre de Recherche des Cordeliers, Paris, France

Submitted 29 April 2010; accepted in final form 20 June 2010

Hancock ML 2nd, Bichet DG, Eckert GJ, Bankir L, Wagner MA, Pratt JH. Race, sex, and the regulation of urine osmolality: observations made during water deprivation. Am J Physiol Regul Integr Comp Physiol 299: R977–R980, 2010. First published June 23, 2010; doi:10.1152/ajpregu.00289.2010.—A more concentrated urine was excreted by blacks than whites and by men than women. The purpose of this study was to explore the physiological bases for the race and sex effects during water deprivation when osmoregulation is challenged and differences are amplified. Drinking water was withheld from 17 blacks (10 men) and 19 whites (9 men) for 24 h. Vasopressin (VP) levels and osmolality in plasma (P_{osmol}) and urine (U_{osmol}) were measured basally and then every 4 h. U_{osmol} was higher in blacks at baseline (P = 0.01) and during water deprivation (P = 0.046). Before and during water deprivation, no differences were seen in levels of VP, P_{osmol}, or the VP-U_{osmol} relationship between blacks and whites. Although VP levels were initially higher in men (P < 0.02 for samples collected over the first 12 h), over the last 12 h of water deprivation, U_{osmol} was higher (P = 0.027) and more responsive to the level of VP (in terms of slopes, P = 0.0001) in women than men. Our results suggest that, after a period of water deprivation, there develops a sensitivity of the collecting duct to VP that is greater in women. Although U_{osmol} is higher in blacks, the race difference in water conservation did not appear to result from differences in the level of VP or the sensitivity of the collecting duct to VP. Upstream effects such as Na⁺ uptake in the thick ascending limb, with its ensuing effects on water reabsorption, need to be considered in future studies of the relationship of race to water conservation.

In the present study, we sought to determine how race and sex modify water balance under conditions when water-conserving processes are challenged. Specifically, we followed a protocol in which subjects consumed no water for 24 h, with the intent to amplify and, thereby, better delineate the basis for the differences in how water is conserved.

MATERIALS AND METHODS

Subjects. Subjects were healthy and taking no medications, with the exception of the women, who used oral contraceptives. Seventeen of the subjects were blacks (10 men) and 19 were whites (9 men); their age range was 18–31 yr. The study was approved by the Institutional Review Board at the Indiana University School of Medicine. All subjects provided written informed consent.

Study design. Subjects collected a urine sample overnight; they were admitted to the Indiana Clinical Research Center on the next morning. They consumed a standard breakfast along with 200 ml of water (no other liquids were permitted). After 10 AM, subjects were not allowed to drink any fluids, and only food low in water content could be consumed. Subjects were not allowed to leave the clinical studies unit; use of nicotine products was not permitted. All urine collected was divided into 4-h aliquots for measurements of electrolytes and osmolality (U_{osmol}). Blood samples were collected every 4 h for measurements of VP, electrolytes, and plasma osmolality (P_{osmol}). After 20 h of water deprivation, each subject received 4 μg of desmopressin [desamino-8-d-arginine vasopressin (dDAVP)] subcutaneously and collected urine for an additional 4 h. After 24 h of water deprivation, each subject was given free access to water, and the volume consumed in 30 min was measured.

Assays. Electrolytes were measured using a COBAS ISE analyzer, and creatinine was measured using a COBAS MIRA analyzer (Roche Diagnostics). P_{osmol} and U_{osmol} were measured with a microosmometer (model 246, Fiske Associates). VP was measured by radioimmunoassay as previously described (7).

Statistical analysis. Analysis of covariance was used for comparing ethnic and sex groups at baseline and during water deprivation at each urine collection point. Repeated-measures analysis of covariance was used for the ethnic and sex comparisons combining all time points into a single analysis to test for overall ethnic and sex effects. Covariates included in the models were age and body surface area. Pearson correlation coefficients were calculated to evaluate the associations between variables. Some of the outcomes were logarithmically transformed to satisfy the distributional assumptions of the ANOVA. Variables that required the transformation included VP levels, urinary Na⁺ excretion, and the volume of water consumed at the end of the study. For the outcomes that required transformation for the analysis, means ± SE were transformed back to the original scale in Figs. 1 and 2.

ON AVERAGE, URINE CONCENTRATIONS are higher in blacks than whites (4) and in men than women (15) for reasons that are not fully understood. A delineation of mechanisms for these differences in how water is conserved might shed light on certain kidney-related disorders such as hypertension, which is more common in blacks (11) and men (16).

The kidney’s capacity to concentrate urine is highly dependent on the level of vasopressin (VP) and the renomedullary osmotic gradient against which water is reabsorbed. VP levels were reported to be higher in blacks than whites in some (2, 8), but not all (9), studies and were higher in men than women (10, 17). Na⁺ reabsorbed in the thick ascending limb (TAL) by the Na⁺-K⁺-2Cl⁻ cotransporter (NKCC2) (13) is an essential osmotic constituent of the gradient. Differences in level of TAL function could be related to the race or sex difference in water conservation.

Address for reprint requests and other correspondence: J. H. Pratt, Indiana Univ., 541 Clinical Dr., Indianapolis, IN 46202 (e-mail: johpratt@iupui.edu).

http://www.ajpregu.org
RESULTS

Subject characteristics. The mean body mass index was marginally higher ($P = 0.052$) in blacks (Table 1). Blood pressure was not significantly different between blacks and whites or between men and women.

VP levels, $P_{osmol}$, $U_{osmol}$, and urine flow rates. VP levels were similar in blacks and whites ($P = 0.25$), except after 4 h of water deprivation, when VP levels were greater in blacks ($P = 0.02$; Fig. 1). $U_{osmol}$ was greater in blacks than whites at baseline [827 ± 58 vs. 614 ± 55 (SE) mosmol/kgH$_2$O, $P = 0.01$] and during the overall period of water deprivation ($P = 0.046$; Fig. 1). Urine flow rates were significantly less in blacks than whites at baseline (35 ± 6 vs. 58 ± 6 ml/h, $P = 0.004$; Fig. 1) and during water deprivation ($P = 0.034$). With respect to comparisons between men and women, VP levels were higher in men than women during the first 12 h of water deprivation ($P = 0.012, 0.0081, 0.52$, and 0.025 at 0, 4, 8, and 12 h, respectively). Although there was no sex difference in $U_{osmol}$ at baseline ($P = 0.86$), during water deprivation $U_{osmol}$ was significantly greater in women than men ($P = 0.027$ for the averages of $U_{osmol}$ over 12–20 h). $P_{osmol}$ was not significantly different between blacks and whites ($P = 0.39$) or between men and women ($P = 0.81$; baseline means shown in Table 1).

dDAVP administered after 20 h of fluid restriction had no significant additional effect on $U_{osmol}$ (Fig. 1); there was no ethnic difference in the response to dDAVP, although urine volumes remained significantly less in blacks after dDAVP ($P = 0.02$).

Effect of race and sex on VP-$P_{osmol}$ and VP-$U_{osmol}$ relationships. The relationship of plasma VP concentration to $P_{osmol}$ was positive in all groups over the last 12 h of water deprivation ($r = 0.36, P = 0.031$); there was no effect of race or sex on the VP-$P_{osmol}$ relationship. The level of VP as a determinant of $U_{osmol}$ was used to examine its effectiveness ("sensitivity"). No effect of race on the VP-$U_{osmol}$ relationship was observed ($P = 0.21$). There was, however, a significant difference in responses in men and women ($P = 0.0001$ when examined over the 12-h period beginning at 8 h and ending at 20 h prior to treatment with dDAVP): the VP-$U_{osmol}$ relationship was positive in women and negative in men ($r = 0.46$ for black women, 0.68 for white women, −0.61 for black men, and −0.63 for white men; Fig. 2).

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Black</td>
<td>White</td>
</tr>
<tr>
<td></td>
<td>($n = 7$)</td>
<td>($n = 10$)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>25.1 ± 1.6</td>
<td>23.1 ± 0.7</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>31.6 ± 2.9</td>
<td>24.0 ± 2.1</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>115 ± 4</td>
<td>117 ± 3</td>
</tr>
<tr>
<td>Diastolic</td>
<td>64 ± 3</td>
<td>69 ± 3</td>
</tr>
<tr>
<td>Vasopressin, pmol/l</td>
<td>0.8 ± 0.3</td>
<td>0.4 ± 0.3</td>
</tr>
<tr>
<td>Osmolality, mosmol/kgH$_2$O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>758 ± 89</td>
<td>708 ± 86</td>
</tr>
<tr>
<td>Plasma</td>
<td>292 ± 4</td>
<td>297 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE. BMI, body mass index.

Post-water deprivation. The cumulated volumes of water excreted during the total 24-h dehydration period were ~20% smaller in blacks than whites in men and women (Table 2). The volumes of water freely consumed over the 30-min period immediately following the water deprivation exhibited no relationship to ethnicity ($P = 0.63$) or sex ($P = 0.25$). There were no race differences in weight loss during water deprivation ($P = 0.81$), but men lost more weight than women ($P = 0.02$). The mean weight loss (kg) for individual groups was 1.4 ± 0.2, 1.3 ± 0.2, 1.8 ± 0.2, and 1.9 ± 0.2 (SE) g for black women, white women, black men, and white men, respectively.
DISCUSSION

To our knowledge, the current study is the first to look at the effects of race and sex on how the kidney conserves water when water for consumption is restricted. The most noteworthy findings were the sex differences. Specifically, over the first 12 h of water deprivation, VP levels were higher in men than women, as previously described (10, 17); this difference may explain the typically more concentrated urines in men than women (15) (in the present study, no baseline difference in Uosmol between men and women was observed, probably because sample sizes were not sufficiently large). After 12 h, however, the male-female difference changed: Uosmol was higher in women and proportional to the VP level, whereas Uosmol was less tightly associated with the VP level in men. Uosmol and VP level were, in fact, positively associated in women and negatively associated in men (Fig. 2). Such a sex difference may have relevance to what has been perceived as a greater propensity of women to develop hyponatremia under certain conditions (1, 18). The reason for this is unclear; however, one study has suggested that estrogens enhance the response of Uosmol to VP (19).

Uosmol was higher at baseline and during water deprivation in blacks than whites. VP levels were the same in the two groups, as was collecting duct sensitivity to VP, leaving us to conclude that the race difference is not mediated by VP. The more intense water conservation in blacks could be explained by a greater renomedullary osmotic gradient, which facilitated water reabsorption from the collecting duct. Although multiple factors, such as prostaglandins and regional blood flow (6, 14), influence the gradient, a principal determinant is the amount of luminal Na\(^+\) reabsorbed by NKCC2 (12). In Bartter’s syndrome, for example, where there is less reabsorption of Na\(^+\) by NKCC2, urine concentrations are low (5). In an earlier study, differences in urinary excretion of cations in blacks and whites in response to administration of furosemide (9), an inhibitor of NKCC2, suggested that, indeed, blacks have a more active TAL. On the other hand, Weder and co-workers (20) concluded from water-loading studies that the TAL may be less active in blacks. However, the two studies considered different aspects of TAL function: the furosemide study (9) examined the contribution of the TAL in the medullary region to the urine concentration, whereas the water-loading study (20) examined the ability to excrete a more dilute urine, which depends on the TAL residing in the cortical region (3).

A limitation to our study was the relatively small number of subjects. It may not have been possible to detect physiologically important small differences in some of the assessments. For example, we did show, at baseline, the sex difference in Uosmol that has been reported by others (15). On the other hand, performing studies in young and healthy subjects in a controlled inpatient environment reduced the variability that could otherwise have been present.

Perspectives and Significance

The more effective water conservation observed in female subjects who were challenged by water deprivation was unanticipated, and its significance is unclear. We speculate that it could have been a residual effect of what was a survival advantage. It might have resulted in a healthier in utero condition and a better lactating capacity when “water deprivation” could have, in fact, been closer to the norm. The finding that VP levels were similar in blacks and whites before and during water deprivation leaves open the possibility of greater Na\(^+\) uptake by the TAL in blacks. This could be the basis for why blacks conserve water more readily than whites, and, perhaps more importantly, it adds to the speculation that

Table 2. Volumes of urine excreted during water deprivation and volumes of water consumed over the 30 min immediately following the end of water deprivation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine volume excreted during water deprivation, ml/24 h</td>
<td>938 ± 87</td>
<td>1,082 ± 74</td>
</tr>
<tr>
<td>Water consumed at the end of water deprivation, ml</td>
<td>558 ± 170</td>
<td>782 ± 144</td>
</tr>
</tbody>
</table>

Values are means ± SE.
increased uptake of Na\(^+\) in the TAL contributes to the risk for hypertension among blacks.

**GRANTS**

This study was supported by the Veterans Health Administration and by National Institutes of Health Grants RO1-HL-35795, RO1-HL-095086, and MO1-RR-750.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**REFERENCES**