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ankir et al. (1) report that young, healthy black individuals concentrate urine significantly more than matched white individuals and excrete lower urine volumes. In addition, they found that, among men, pulse pressure was significantly higher in normotensive black individuals than in white individuals, although there was no significant difference in systolic and diastolic BP. These findings refocus attention on vasopressin as a hypertensive hormone, however with a new mechanistic twist and a novel interpretation of an ethnic difference. Bankir et al. also report a direct association between urine concentration and pulse pressure in men but not in women. Again, the correlation coefficient was stronger in black men than in white men. This early difference may be important because elevated pulse pressure is associated with an increased risk for cardiovascular events. The authors suggest that vasopressin could contribute to hypertension via its antidiuretic effects and that vasopressin V2 receptor antagonists might lower BP. Possibly, vasopressin plays a greater role in individuals with blunted renin-angiotensin system, as is the case in black individuals. Acutely, this notion has experimental support (2).

In their analysis, Bankir et al. (1) relied on a data set that was generated at Indiana University Medical Center 35 yr ago. Neither urine osmolarity nor vasopressin was measured in the Indiana University protocol. Nevertheless, the studies were performed meticulously on a metabolic ward. The patients were in similar states of electrolyte intake, and the BP measurements were controlled carefully. Such broad-based metabolic studies can never be performed again, so data dredging (now termed “data mining”) for the purpose of hypothesis generation is a legitimate enterprise. In this case, the data that were collected allowed the a posteriori calculation of a urine concentration index. Another data set that would be amenable for examination of this hypothesis further could be provided by the International Study of Sodium, Potassium, and Blood Pressure (INTERSALT) study (3). In INTERSALT, more than 10,000 people were studied worldwide with meticulous 24-h urine collections and random-zero BP measurements. Urine volume, electrolyte, creatinine, and urea excretion were measured in every individual, allowing a more precise calculation of urine solute excretion and concentration. With this data set, a more precise analysis of any relationships among urine concentration, sodium concentration, urine volume, and BP could be performed. Gender differences and ethnic comparisons also could be examined if only the INTERSALT investigators would accept external analyses of their data set.

Support for the authors’ idea is provided by another recent study by Bankir et al. (4) that reported that V2 receptor stimulation reduces sodium excretion in normal humans. In that study, infusion of a V2 receptor agonist, dDAVP, reduced sodium excretion concomitantly with an increase in urine osmolality and a decrease in urine volume. The inclusion of patients with central diabetes insipidus, V2 receptor mutations, or aquaporin-2 mutations provided an elegant control. The authors raised the notion that vasopressin might reduce sodium excretion by increasing epithelial sodium channel expression and activity as demonstrated in rats (4) and proposed that this effect might represent an adaptation to improved water conservation (1).

Nonetheless, the vasopressin-to-hypertension hypothesis has had tough sledding, even though dDAVP administration to rats over weeks increases BP by 10 mmHg and can make desoxycorticosterone-salt hypertension worse (5). The literature is extensive and cannot be reviewed in detail here. Renal medullary blood flow has an important impact on BP regulation (6). Vasopressin may influence renal medullary blood flow via V1a receptors. Cowley et al. (6) investigated the effects of vasopressin infusion into the renal medulla chronically. Uninephrectomized Sprague-Dawley rats were prepared with implanted renal cortical and medullary optical fibers for daily measurements of cortical and medullary blood flow using laser-Doppler flowmetry techniques. Vasopressin produced only an initial, nonsignificant reduction of medullary blood flow and failed to raise arterial pressure significantly (7). It is interesting that the same group showed that a selective V1 agonist ([Phe2,Ile3,Orn8]vasopressin) can chronically increase BP in the rat (8). However, vasopressin also stimulates release of nitric oxide probably via extrarenal stimulation of V2 receptors and subsequent nitric oxide synthase activation. These effects likely buffer against the hypertensive actions of vasopressin. Acute infusion of vasopressin is known to increase BP transiently, but acute infusion of the selective V2 agonist dDAVP lowers it (4). Therefore, an imbalance between the intensity of vasoconstrictive V1a and nitric oxide–generating V2 effects could be ex-
pected to alter BP regulation. Ganten et al. (9) developed a strain of spontaneously hypertensive rats that also are homozygous for central diabetes insipidus (Brattleboro strain). The rats developed hypertension nonetheless, even though their vasopressin concentrations are zero, thereby showing that vasopressin actions are not a prerequisite in all forms of hypertension.

Could increased water intake counteract the effects of vasopressin? A well-accepted health homily is to “drink plenty of water and keep yourself on schedule.” Acute water drinking (500 ml in 30 min) has independent cardiovascular and metabolic effects in patients with autonomic failure and normal older individuals but not in healthy individuals, except when exposed to phenylpropanolamine (10). This acute increase in BP does not necessarily contradict the hypothesis raised by Bankir et al. (1), which addresses long-term consequences of the vasopressin/thirst axis. The effects of chronic increased water intake on BP in normal or hypertensive individuals have not been studied but should be. In five-sixths nephrectomized rats, chronic increase in water intake reduced BP and urinary albumin excretion despite an increase in plasma renin activity (11).

What sort of prospective studies could Bankir et al. perform to test their hypothesis directly? Metabolic ward investigation of healthy black and white individuals but not in healthy individuals, except when exposed to phenylpropanolamine (10). This acute increase in BP does not necessarily contradict the hypothesis raised by Bankir et al. (1), which addresses long-term consequences of the vasopressin/thirst axis. The effects of chronic increased water intake on BP in normal or hypertensive individuals have not been studied but should be. In five-sixths nephrectomized rats, chronic increase in water intake reduced BP and urinary albumin excretion despite an increase in plasma renin activity (11).

Disclosures

None.

See the related article, “Ethnic Differences in Urine Concentration: Possible Relationship to Blood Pressure,” on pages 304–312.

The excellent review in this month’s issue of JASN by Fenton and Knepper on urea and renal function in the 21st century (pages 679–688) as well as the editorial by Sands about the critical role of urea in the urine concentrating mechanism (pages 670–671) should be of interest to readers of CJASN who have been provided with data regarding ethnic differences in urine concentration and their relationship to blood pressure by Bankir et al. (pages 304–312). In addition, the editorial by Luft in CJASN provides perspective on these findings including vasopressin’s role in urinary concentration.

References


