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Sodium intake affects gender difference in aldosterone concentration

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Basic and clinical studies alike have demonstrated significant gender differences in the renin-angiotensin-aldosterone system (RAAS), a major regulator of electrolytes, fluids and blood pressure in the body. For instance, it was reported in humans that healthy male subjects have higher aldosterone concentrations than healthy female subjects, which induces greater sodium and water retention in men (6). However, it is unclear whether these gender differences in aldosterone concentrations are associated with gender differences in extracellular volume. In addition, although we know that factors such as salt intake and menstrual cycle affect the RAAS (10), we do not know whether these factors affect the consistency of RAAS-related gender differences across different situations in humans.

In this issue of the American Journal of Physiology-Renal Physiology, Toering et al. study aldosterone-related gender differences under standardized conditions in healthy human subjects (11). They record the phase of the women's menstrual cycle and measure aldosterone concentrations, blood pressure and extracellular volume under controlled low and high sodium intake conditions in men and women. They report that women have lower extracellular volume and blood pressure than men, and suggest that aldosterone could induce these gender differences because women have lower aldosterone concentrations and a high adrenal response to angiotensin II. Another important finding from this study is that dietary sodium intake significantly affects gender differences in aldosterone concentrations. Interestingly, men had higher aldosterone concentrations than women under conditions of high sodium intake but not low sodium intake, while gender differences in blood pressure,

extracellular volume, and adrenal response to angiotensin II persisted under both low and high sodium dietary intakes. This indicates that dietary status should be considered in relation to previous and future RAAS-related gender difference research. This may reveal novel interpretations of the relationship between sodium and RAAS-related gender differences, which may inform strategies for RAAS inhibitor therapy.

The authors clearly demonstrate gender differences in aldosterone and extracellular volume; however, the underlying mechanisms and associations remain to be clarified. Under high sodium intake conditions, there is a significant correlation between aldosterone concentration and extracellular volume. Conversely, there was no such significant correlation or gender difference in aldosterone concentration under low sodium intake conditions. Low aldosterone concentrations in women could therefore explain the gender difference in extracellular volume under conditions of high sodium intake but not low sodium intake, suggesting that something other than aldosterone regulates the gender difference in extracellular volume when salt intake is low. Potential regulators of extracellular volume under low sodium intake conditions include androgen, estrogen and the sympathetic nervous system (1, 4, 9). Further basic and clinical studies are required to elucidate the detailed mechanisms underpinning gender differences in aldosterone and its control of extracellular volume. However, the question of why high sodium intakes accentuate the gender difference in aldosterone concentration remains. At present there is no clear answer, so this question must be addressed by future studies. It is possible, however, that the current study may not have been able to detect a gender difference in

aldosterone concentration under low sodium intake conditions because of the sampling protocol. A long-term salt and water balance study in healthy human subjects found that daily urinary aldosterone excretion exhibits a longer infradian rhythm and marked day-to-day fluctuations that are independent of sodium intake (7, 8). This long-term study measured daily urinary aldosterone excretion for more than 100 days, whereas the current study measured aldosterone concentration at one timepoint only. The former study also showed that the range of day-to-day rhythmical urinary aldosterone excretion was over 20 μg per day, suggesting that measurement of aldosterone from a single timepoint might not be enough to detect a small difference in aldosterone concentration between two groups (7, 8, 11). Therefore, the authors might not have been able to detect a gender difference in aldosterone concentration under low sodium intake conditions because of nature of the day-to-day rhythmical secretion of aldosterone. Notably, this paper did show gender differences in the adrenal response to angiotensin II under both high and low sodium intake conditions, despite similar aldosterone concentrations between men and women under low sodium intake.

RAAS inhibitors are currently one of the major medicines used for the treatment of hypertension. On the basis of the Toering et al. study, gender effects of RAAS inhibitors should be considered in the treatment of hypertension. Women have lower aldosterone concentrations, extracellular volume, and blood pressure than men (11), indicating that RAAS inhibitors are likely to be less efficient in women than men. In fact, previous studies suggested that men responded better to RAAS inhibitors than women (2) and that there was a

gender difference in the response to angiotensin converting enzyme inhibitors and angiotensin receptor blockers (3). However, this study was performed in healthy subjects only, and we do not know the nature of aldosterone-related gender differences in hypertensive patients. This pathological condition may affect gender differences in the RAAS, and there may be gender effects of RAAS inhibition that differ from underlying gender differences in the RAAS. Indeed, we and another group have reported that an angiotensin receptor blocker and estrogen synergistically protect vessels after vascular injury (5, 12). These findings suggest that women receive better vasoprotective activity from an angiotensin receptor blocker than men. Future studies on gender differences in the RAAS in hypertensive patients, including the effects of the RAAS inhibitors, promise to be very interesting.

Toering et al. (11) elegantly demonstrate the gender differences in aldosterone concentration and their association with extracellular volume in the current issue, and this study will no doubt prompt further gender difference-rerated basic and clinical studies in this area. We hope that this research will further the understanding of body fluid control in humans and lead to more efficient hypertension therapies using RAAS inhibitors.

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DISCLOSURE

The authors have no conflicts of interest to disclose, financial or otherwise.

AUTHOR CONTRIBUTIONS

K.K. and A.N. wrote the manuscript.

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