EDITORIAL FOCUS

Sodium intake affects sex difference in aldosterone concentration

Kento Kitada and Akira Nishiyama
Department of Pharmacology, Faculty of Medicine, Kagawa University, Kagawa, Japan

BASIC AND CLINICAL STUDIES ALIKE have demonstrated significant sex 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 sex differences in aldosterone concentrations are associated with sex 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 sex differences across different situations in humans.

In a recent issue of the American Journal of Physiology-Renal Physiology, Toering et al. study aldosterone-related sex differences under standardized conditions in healthy human subjects (11). They record the phase of the women’s menstrual cycles 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 sex 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 sex differences in aldosterone concentrations. Interestingly, men had higher aldosterone concentrations than women under conditions of high sodium intake but not low sodium intake, whereas sex 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 sex difference research. This may reveal novel interpretations of the relationship between sodium and RAAS-related sex differences, which may inform strategies for RAAS inhibitor therapy.

The authors clearly demonstrate sex 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 sex difference in aldosterone concentration under low-sodium intake conditions. Low aldosterone concentrations in women could therefore explain the sex difference in extracellular volume under conditions of high sodium intake but not low sodium intake, suggesting that something other than aldosterone regulates the sex 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 sex differences in aldosterone and its control of extracellular volume. However, the question of why high sodium intakes accentuate the sex 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 present study may not have been able to detect a sex 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 >100 days, whereas the present study measured aldosterone concentration at one time point only. The former study also showed that the range of day-to-day rhythmic urinary aldosterone excretion was over 20 μg per day, suggesting that measurement of aldosterone from a single time point 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 sex difference in aldosterone concentration under low-sodium intake conditions because of the nature of the day-to-day rhythmic secretion of aldosterone. Notably, this paper did show sex 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, sex 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 in men. In fact, previous studies suggested that men responded better to RAAS inhibitors than women (2) and that there was a sex 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 sex differences in hypertensive patients. This pathological condition may affect sex differences in the RAAS, and there may be sex effects of RAAS inhibition that differ from underlying sex 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 sex 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 sex differences in aldosterone concentration and their association with extracellular volume in the present issue, and this study will no doubt prompt further sex difference-related 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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