Aldosterone Paradox
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I was fascinated to read the article by Arroyo et al. (1) that addressed the aldosterone paradox. With available information on the fine details of the diverse receptors along the distal nephron that are involved in sodium and potassium homeostasis, the authors have formulated an elegant working model of how, in response to hypovolemia, the body conserves sodium without a secondary hyperkaliuria. Conversely, in hyperkalemia, the body promotes urinary potassium loss with no retention of sodium and fluid. The central player in these mechanisms was proposed to be angiotensin II (AII) activation of the WNK4 regulator acting in conjunction with both AII and aldosterone in hypovolemia, but in hyperkalemia the sole action of aldosterone produced its effect without the differential actions of AII on ROMK or NCC channels.

I remember reading a useful teaching article by Arthur Vander (3) that highlights areas of conceptual difficulties in renal physiology that are commonly encountered by students (and lecturers), including this aldosterone paradox. Physiologically, the homeostatic resolution of hypovolemia should not result in a secondary hypokalemia. In hypovolemia, the overall neuro-hormonal, whole body response emphasized by Vander is still essential to appreciate. Hypovolemia leads to baro- and volume-activated renal sympathetic activity. The GFR is decreased by renal arteriolar vasoconstriction, and thus the filtered load of sodium is reduced as part of sodium conservation. In addition, both sympathetic nerve and AII also directly increased sodium reabsorption at the proximal tubule where sodium recovery normally accounts for ~70% of the total filtered sodium load, accompanied by a proportionate iso-osmotic reabsorption of water. Glomerulo-tubular balance through changes during hypovolemia in intrarenal hemodynamics also participates in increasing sodium/fluid reabsorption. This major upstream effect on sodium and water handling at the proximal nephron should always be considered and integrated into downstream fine regulation at the distal nephron. In hypovolemia, the compensatory reduction in both tubular fluid and sodium delivered downstream to the distal nephron thus contributes to countering the potential increased tubular secretion of potassium when aldosterone acts during hypovolemia. The flow-dependent potassium BK channels would thus be involved beside the differential effects of AII on NCC and ROMK in Arroyo’s model.

This integration of fine cellular mechanisms with whole body physiology is necessary, as rightly highlighted in Dr. Joyner’s comment in the same issue of Physiology (2).

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References