Landscape of ENaC regulation in the kidney

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AS THE REAL ESTATE MAXIM GOES, “There are three things that matter in property: location, location, location.” The same could be said about epithelial Na+ channel (ENaC) regulation in the mouse kidney. ENaC is an heteromeric ion channel (comprised of α-, β-, and γ-subunits) expressed in the aldosterone-sensitive distal nephron (ASDN) and provides the final conduit for Na+ reabsorption from the tubular fluid before it becomes urine. Transgenic mouse models and persons with Mendelian forms of hypertension (or hypotension) demonstrate that dysregulation of ENaC activity can lead to profound effects on extracellular fluid (ECF) volume status and blood pressure. Gain of function mutations in genes encoding either the β- or γ-subunits of ENaC lead to renal Na+ retention and hypertension; conversely, loss of function mutations in any of the three ENaC subunits leads to severe symptoms or even death from either impaired lung water clearance or renal Na+ wasting, hyperkalemia, and hypotension.

Perhaps because ENaC is in such a strategic position to modify the ionic composition of the tubular fluid, it is subject to extensive regulation by a panoply of factors, including hormones, proteases, and mechanical stimuli. Aldosterone is a key mineralocorticoid hormone secreted by the adrenal gland in response to decreases in plasma volume and raises ECF volume and blood pressure by increasing expression and activity of ENaC in the apical plasma membrane of tubular epithelial cells of the ASDN. The extent to which ENaC localizes to the apical membrane of the ASDN, defined as the late distal convoluted tubule (DCT2), collecting segment (CNT), and the collecting duct (CD), depends on the nephron segment and level of dietary Na+ intake. When mice are fed a regular-Na+ diet, apical localization of ENaC is restricted to the DCT2 and CNT (8). When mice are fed a low-Na+ diet, which raises the plasma aldosterone concentration, apical localization of ENaC expands from the DCT2 to the CD (8).

Recent characterization of two different conditional α-ENaC knockout mouse models reveals that location matters: the site of ENaC deletion is a critical factor in determining whether affected mice develop urinary Na+ wasting and ECF volume depletion. Mice with cell-specific deletion of α-ENaC from the CD maintain Na+ and water balance, even when placed on dietary Na+ restriction (11). In contrast, mice with cell-specific deletion of α-ENaC from the late CNT through the CD exhibit urinary Na+ wasting and weight loss (2). These findings indicate that the CNT is a critical site for ENaC-mediated Na+ reabsorption and suggest that deletion of ENaC expression in the CNT is sufficient to alter Na+ balance in mice. From an anatomical perspective, the capacity for ENaC-mediated Na+ reabsorption is much higher in the CNT because in part the luminal surface area for Na+ reabsorption in the CNT is much greater, with approximately five CNT feeding into each CD in rodent kidney (4, 6, 12). Interestingly, ENaC activity in the rat CNT is also higher on a per-cell basis than in the CD (4), suggesting that regulation of ENaC activity is different in the early and late segments of the ASDN.

In an issue of the American Journal of Physiology-Renal Physiology, Nesterov et al. (10) report that aldosterone-mediated regulation of ENaC is indeed distinct in the transition zones of mouse DCT2/CNT and CNT/CD, even though the biophysical properties of ENaC in these nephron segments are similar. Single channel and whole cell current recordings in split-open tubule preparations were performed to investigate ENaC activity in the DCT2/CNT and CNT/CD after mice were fed diets of differing Na+ composition. In the DCT2/CNT, basal ENaC activity (amiloride-sensitive whole cell current) was high, even when mice were fed either a regular- or high-Na+ diet to suppress plasma aldosterone (10). In contrast, in the CNT/CD, basal ENaC activity was low compared with that in the DCT2/CNT, but ENaC activity in the CNT/CD increased robustly when mice were placed on dietary Na+ restriction (10). To definitively rule out the role of aldosterone in maintaining ENaC activity in the DCT2/CNT, the authors performed a similar set of experiments in aldosterone synthase knockout (AS KO) mice, which have no detectable levels of plasma aldosterone concentration (7). Not unexpectedly, dietary Na+ restriction led to an increase in ENaC activity in the CNT/CD of wild-type but not in AS KO mice (10). However, ENaC activity in the DCT2/CNT of AS KO mice was high and did not change when mice were fed either a regular- or low-Na+ diet (10), confirming that aldosterone is not required for ENaC activity in the DCT2/CNT.

If findings from this study can be extrapolated to humans, the clinical implications are twofold. First, the roles of ENaC in the DCT2/CNT and CNT/CD in regulating Na+ balance may be distinct. ENaC in the DCT2/CNT, with its high basal activity and resistance to changes in plasma aldosterone concentration, constitutively drives Na+ reabsorption from the tubular fluid. This population of ENaC channels contributes to baseline Na+ reabsorption and ECF volume maintenance and not necessarily to the defense against ECF volume depletion. In contrast, ENaC in the CNT/CD, with its low, but modulatable, activity, rapidly and potently increases Na+ reabsorption from the tubular fluid under conditions of ECF volume depletion (e.g., after Na+ restriction). Second, as Nesterov et al. aptly point out (10), there may be benefit in treating hypertensive individuals with amiloride to inhibit ENaC channels in the DCT2/CNT, even if these individuals are ingesting a diet that is rich in Na+ content (i.e., the typical Western diet), since ENaC in this nephron segment is resistant to changes in plasma aldosterone concentration. Furthermore, in individuals with hypertension driven by a high-aldosterone state, a regimen that includes spironolactone and/or amiloride could also be effective because it would inhibit the entire population of ENaC activity in the kidney.
ENaC channels in the ASDN. While amiloride is largely neglected in modern clinical practice, there is good evidence for the benefit of amiloride, used in combination with a thiazide diuretic, in saving lives and reducing the incidence of stroke in hypertensive patients (1, 3, 5, 9).

The findings from Nesterov and colleagues break new ground in identifying a mode of regulation of ENaC in the DCT2/CNT that is independent of aldosterone and prompt new questions regarding the hormonal, molecular, and cellular mechanisms underlying the differential regulation of channels located in the DCT2/CNT and CNT/CCD. Other hormones that are known to stimulate ENaC activity, including glucocorticoids, insulin/insulin growth factor 1, arginine vasopressin, and angiotensin II, may play significant roles in regulating ENaC activity in the DCT2/CNT. In real estate, identifying factors that drive the desirability of a location is an important part of the home buying process. Similarly, identifying the physiological stimuli and regulatory processes that control ENaC activity in different segments of the ASDN, particularly in the DCT2/CNT, will be critical for understanding the segment-specific functions of ENaC in regulating total body Na\(^{+}\)/K\(^{+}\) balance.

REFERENCES


