Renal Sodium Handling: The Role of the Epithelial Sodium Channel

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The epithelial sodium channel (ENaC) is a critically important final regulator of the balance between intake and excretion of dietary sodium (1), and along with the thiazide-sensitive NaCl co-transporter constitutes the predominant sodium transport systems in the aldosterone-sensitive distal nephron (2). The use of the oocyte expression system for cloning the ENaC subunits was a technical tour de force by Canessa et al. (3,4). As proposed by Guyton (5), and confirmed by the unraveling of the activating ENaC mutations in Liddle’s syndrome (6), dysregulation of the final balance of sodium intake and excretion can result in chronic volume expansion, plasma renin suppression, and arterial hypertension (1). In the intervening years since the description of the three ENaC subunits, a wealth of information has been published about the effects of the gain-of-function mutations in both ENaC and the mineralocorticoid receptor (pseudoaldotersonism) and the loss-of-function mutations in both (pseudohypoaldosteronism) on classically described human disease states (7).

Our purpose in assembling this Frontiers in Nephrology section on the physiology and pathophysiology of ENaC is to provide a concise synopsis of the current state-of-the-art, knowing full well that any such effort is forced to be selective and also runs the risk of loss of timeliness in a rapidly developing field such as the study of ENaC. Nevertheless, the contributions in this Frontiers edition represent the signal areas of this field and have been superbly crafted by authors who have been on the front lines of these developments.

The use of knock-out (and knock-in) mouse models of human disease states have been fertile soil for exploring the tissue-specific expression of ENaC, and has brought the most current molecular techniques to bear on understanding the distribution and regulation of ENaC activity. The second article in this issue’s Frontiers is a review by Hummler and Vallon (8) that summarizes both the loss-of-function and gain-of-function mutations at a functional level. The gene-targeting approaches have generated models that control the genetic defects in a time- and tissue-dependent conditional or constitutive manner. Surprises have emerged along the way, most strikingly the understanding of the spectrum of transport activities along the aldosterone-sensitive distal nephron, which have expanded our thinking beyond the classic collecting duct paradigm.

Blacks often have low-renin, salt-sensitive hypertension, which could be explained by some sort of persisting activation of ENaC, even in the face of relatively excessive dietary salt intake (9). Despite initial enthusiasm for finding causative mutations in the ENaC subunits in this common condition, Liddle’s syndrome remains a fascinating but extremely rare cause of human hypertension. The possibility that polymorphisms in the three ENaC subunits could contribute to this apparent activation of ENaC (10), and the utility of amiloride as an ENaC-blocker in black hypertension, have been previously considered (11).

In the first contribution to this Frontiers, Howard Pratt (12) summarizes his systematic investigation of the effects of amiloride, spironolactone, and their use in combination, in a short-term randomized, placebo-controlled cross-over study in
polymorphisms in the ENaC subunits.

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The last three contributions in this series drill down on ENaC physiology at the most basic level (18–20). If dysregulation of ENaC activity is somehow involved in human low-renin hypertension as implied by Pratt’s studies (12), structural changes or polymorphisms in the ENaC subunits per se cannot be directly linked to this exceedingly common form of human hypertension, then there may be major gene effects in the ENaC regulation processes, at the translational or posttranslational level, that could explain the underlying pathophysiology of low-renin hypertension. As a prelude to formal linkage studies, the description of the functional domains of ENaC and its regulatory processes are an essential next step. The contribution of Loffing and Schild (18) is a superb summary of the incredibly detailed knowledge that has accumulated about the functional domains of the ENaC complex and the interactions between the subunits. The physical basis of the channel pore and the gating domains, and the domains that interact with transported cations and Na-channel blockers, are being unraveled with exquisite, molecular detail. The regulation by kinase cascades and the interacting intracellular protein constituents of the regulatory networks are details in the review by Staub and Verrey (20). Most notable are the contributions of the Sgk kinase cascade to regulation of channel activity, and the elegant studies defining the interactions of the PY domains of the β- and γ-ENaC subunits with the Nedd4/Nedd4-like ubiquitin-protein ligase family. Understanding the factors that regulate the “dwell-time” of the ENaC complex at the apical membrane, as well as the factors that acutely regulate channel activity at the single channel level, are topics of tremendous basic importance and clinical relevance. In this light, the focus on the inner membrane lipid leaflet and its rapid remodeling in response to kinase cascades and other regulatory factors, summarized by Ma and Eaton (19), are exciting new frontiers in the study of ENaC.

As a final and very personal note, we would like to dedicate this entire Frontiers in Nephrology segment to the memory of Isidore Samuel Edelman. Qais Al-Awqati (21) has written a lovely tribute that captures Izzy’s warmth, enthusiasm, and love for science. Everyone who every worked with Izzy (the “Edelites”) has his or her favorite anecdote that describes his humanness, brilliant imagination, and over-arching view of the field. We hope that Izzy would be thrilled to see how the basic understanding of ENaC physiology has been brought to bear on human disease. He was well known for ending many grant applications with a summarizing statement along the lines of: “Thus, these critically important studies of the toad bladder will help us understand the basis of human hypertension.” Progress is indeed being made, just as Izzy had promised it would be.

References

S: Racial difference in the activity of the amiloride-sensitive epithelial sodium channel. *Hypertension* 40: 903–908, 2002


