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ISN Forefronts Symposium 2015: Maintaining Balance Under Pressure—Hypertension and the Proximal Tubule

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Renal control of effective circulating volume (ECV) is key for circulatory performance. When renal sodium excretion is inadequate, blood pressure rises and serves as a homeostatic signal to drive natriuresis to re-establish ECV. Recognizing that hypertension involves both renal and vascular dysfunction, this report concerns proximal tubule sodium hydrogen exchanger 3 (NHE3) regulation during acute and chronic hypertension. NHE3 is distributed in tall microvilli (MV) in the proximal tubule, where it reabsorbs a significant fraction of the filtered sodium. NHE3 redistributes, in the plane of the MV membrane, between the MV body, where NHE3 is active, and the MV base, where NHE3 is less active. A high-salt diet and acute hypertension both retract NHE3 to the base and reduce proximal tubule sodium reabsorption independent of a change in abundance. The renin angiotensin system provokes NHE3 redistribution independent of blood pressure: The angiotensin-converting enzyme (ACE) inhibitor captopril redistributes NHE3 to the base and subsequent angiotensin II (AngII) infusion returns NHE3 to the body of the MV and restores reabsorption. Chronic AngII infusion presents simultaneous AngII stimulation and hypertension; that is, NHE3 remains in the body of the MV, due to the high local AngII level and inflammation, and exhibits a compensatory decrease in abundance driven by the hypertension. Genetically modified mice with blunted hypertensive responses to chronic AngII infusion (due to lack of the proximal tubule AngII receptors interleukin-17A or interferon-γ expression) exhibit reduced local AngII accumulation and inflammation and larger decreases in NHE3 abundance, which improves the pressure natriuresis response and reduces the need for elevated blood pressure to facilitate circulating volume balance.

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In 1909, Ernest Starling published his lectures in *The Fluids of the Body*.[1] In this monograph, Starling outlines his thoughts on the relationship between body fluid balance, blood circulation, central venous pressure, and cardiac performance. Importantly, renal control of body fluid balance is viewed as key for circulatory and cardiac performance:[1]

> Change in the blood flow through the kidney may bring about alterations in the flow of urine quite irrespective of the composition of the blood or of the tissues. The occurrence of these two classes of phenomena seems to be determined by the fact that the kidney is a dual organ, and that while one part of it acts, so to speak, passively in response to force impressed upon it from without, another part, endowed with sensibility, reacts to external forces in a direction which may be opposed to these forces, but is in all cases the appropriate one for the welfare of the whole organism.

In 1963, Borst and Borst-de Geus[2] discussed hypertension in light of Starling's theory of circulatory homeostasis and postulated that blood pressure rises as a homeostatic reaction to deficient sodium excretion; that is, pressure rises to reestablish sodium balance (at the expense of persistently elevated blood pressure).[2] This response, known as pressure natriuresis, has been reviewed from various perspectives by many investigators.[3,4–7] Figure 1 shows central blood pressure as a function of the ECV and cardiac output as well as the kidneys' regulation of sodium chloride and water reabsorption. A kidney's decision to excrete sodium chloride and water is a function of mediators and controls, both extrarenal and intrarenal, that affect the

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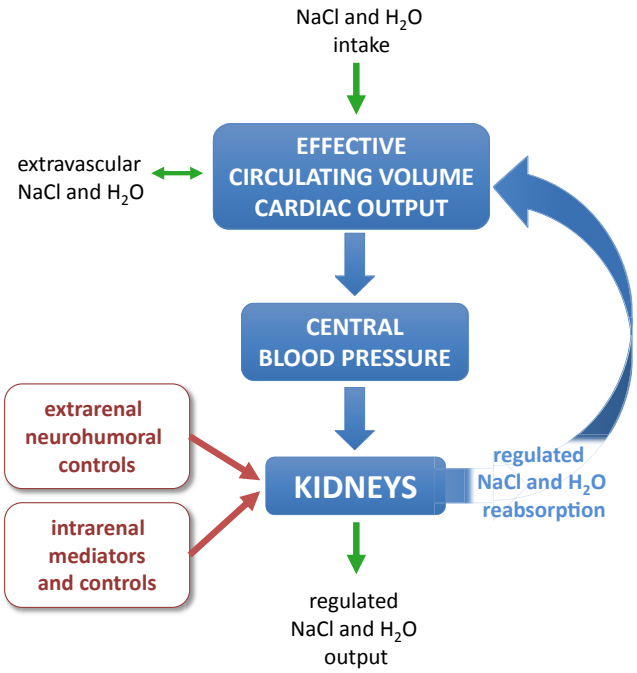

Figure 1. Central blood pressure shown as a function of the effective circulating volume and cardiac output as well as the kidneys' regulation of sodium chloride (NaCl) and water (H_2O) reabsorption, adapted from Starling[1] and Borst and Borst-De Geus.[2] A kidney's willingness to excrete NaCl and water when blood pressure rises is a key controller of the effective circulating volume and blood pressure. This article examines factors, both extrarenal and intrarenal, that reduce this willingness in the proximal tubule (and mechanisms involved), leading to an elevation in blood pressure and activation of pressure natriuresis mechanisms in the proximal tubule that contribute to maintenance of effective circulating volume homeostasis.

rise in blood pressure, as well as the extravascular storage of sodium (discussed in an accompanying report in this series).[8]

Hypertension is the leading cause of stroke and cardiovascular diseases affecting 30% of the adult population in Western cultures.[9] Blood pressure can be elevated by vasoconstriction or by increasing ECV. Excess sodium reabsorption raises ECV and blood pressure, yet, according to Guyton,[3] kidneys have the capacity via pressure natriuresis to excrete enough sodium and volume to normalize blood pressure in the face of expanded ECV. Hypertension was classically viewed as a failure of pressure natriuresis; however, a recent discussion of the role of kidneys in the pathogenesis of hypertension[10] concluded that for hypertension to become chronic there must be impairment of both renal output of salt and water as well as dysfunction of peripheral vascular tone; for example, a failure of peripheral vasodilation due to arterial stiffness. Support for the latter is provided by recent studies illustrating a positive feedback loop wherein arterial stiffening leads to more arterial stiffening.[11]

Although appreciating these complex interactions of body fluids, cardiac output, vascular stiffness, and blood pressure, this report will focus on the regulation of the renal proximal tubule NHE3 as a case-in-point mediator of the pressure natriuresis response, specifically regulation of NHE3 trafficking and abundance, our understanding of how renal dysfunction resets NHE3 regulation to higher pressures, and strategies that may be exploited to improve pressure natriuresis.

Proximal Tubule NHE3 Regulated by Redistribution Within the MV

As reviewed by Palmer and Schnermann,[12] the proximal tubule reabsorbs two-thirds of the salt and water filtered at the glomerulus (120 ml/min) and NHE3 is the main sodium transporter driving transcellular reabsorption in this region. The proximal tubule is a leaky epithelium well built to reabsorb the ~80 ml/min filtrate. As illustrated in the cross-section of the electron micrograph in Figure 2, the proximal tubule has an apical pole covered with a tall brush border of MV each scaffolded by an actin filament core bundled by villin. This specialization increases the surface area for reabsorption more than 30-fold.[13] The apical MV contain water channels as well as many different transporters to reabsorb cations, anions, and substrates from the filtrate. Importantly, a significant fraction of the filtered salt and water is reabsorbed via a paracellular route by claudins.[14]

Membrane transporters and channels can be regulated by trafficking between plasma membrane and intracellular membranes, altered total pool size, covalent modifications such as cleavage or phosphorylation, or protein–protein interaction. Once NHE3 is localized to the proximal tubule MV, there is scant *in vivo* evidence for regulated trafficking between MV and intracellular pools. Rather, NHE3, localized to ordered lipid domains (rafts) in the MV, redistribute between the body and the base of the MV, moving in the plane of the microvillar membranes, likely driven by the atypical molecular motor myosin VI.[15–17] This redistribution from one location to another, rather than degradation and synthesis, facilitates rapid continuous adaptation to changing salt intake, ECV, and/or blood pressure. Figure 2 illustrates the simple case of NHE3 regulation in the transition between normal and high-salt diets in the absence of any change in blood pressure.[18] Figure 2a illustrates that this natriuresis occurs without any change in NHE3 total abundance. Figure 2b shows cross-sections of proximal tubules in a model and in an electron micrograph illustrating organization of dense apical MV. NHE3 redistribution along the proximal tubule MV is detected by colabeling the actin bundling protein villin (red V) and NHE3