Plasmin and Sodium Retention in Nephrotic Syndrome

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Epithelial Na⁺ channels (ENaC) are found within the most distal aspects of the nephron, where they serve as a final arbitrator of the reabsorption of filtered Na⁺. This process has a critical role in the regulation of extracellular fluid volume and BP. Edema-forming states, including cirrhosis, heart failure, and nephrotic syndrome, are associated with enhanced renal Na⁺ absorption. Aldosterone has a role in renal Na⁺ retention in these disorders; however, Na⁺ retention in nephrotic syndrome as a result of activation of Na⁺ absorptive processes in the distal nephron may occur by aldosterone-independent mechanisms.¹ ²

A number of factors that activate ENaC have been described, including cleavage of ENaC subunits by proteases.³ The α and γ subunits are cleaved by proteases in specific regions within their extracellular domains. By cleaving subunits at least twice, inhibitory tracts are released and channels are activated.⁴ ⁵ ENaC is moderately activated when cleaved by furin, a protease that resides in the trans-Golgi network, as the α subunit is cleaved twice by furin releasing an inhibitory tract. In contrast, the γ subunit is cleaved only once by furin. A second cleavage event distal to the γ subunit furin site is needed to activate the channel fully.⁶ ⁷ Studies by Svenningsen et al.⁸ in this issue of JASN, as well as recent work from our group,⁹ provide evidence that plasmin may function as the second protease that cleaves the γ subunit and activates ENaC in the setting of nephrotic syndrome.

Both plasminogen and plasmin are present in nephrotic urine,⁸ ¹⁰ suggesting that plasminogen is filtered by a damaged glomerulus. Plasminogen is cleaved to its active form, plasmin, by various proteases, including urokinase. The presence of urokinase within the tubular lumen of the nephron facilitates the processing of filtered plasminogen to an active form.⁸ ¹¹ ¹² Plasmin joins a growing list of proteases that cleave the γ subunit at sites distal to the furin cleavage site and activates ENaC in association with release of an inhibitory tract.⁵ ¹³

These observations provide new insights regarding a mechanism for renal Na⁺ retention in nephrotic syndrome. They also raise a number of questions that will need to be addressed in future studies. Because amiloride inhibits both ENaC and urokinase, is it effective in ameliorating renal Na⁺ retention and volume expansion in nephrotic syndrome in humans? If plasmin is the activation culprit, then are renal Na⁺ retention and volume expansion in nephrotic syndrome prevented by plasmin inhibitors or by a lack of plasminogen expression (plasminogen knockout mouse model)? Although nephrotic syndrome occurs in the setting of various disorders, is the presence of plasminogen and plasmin in the urine a common finding, or is it restricted to subsets of individuals with nephrotic syndrome? Are there other clinical disorders whereby disease-specific proteases cleave and activate ENaC? With regard to this last question, enhanced ENaC proteolysis may contribute to enhanced ENaC activity in the airways of individuals with cystic fibrosis.¹⁴ ¹⁵

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Phosphorus and Survival: Key Questions That Need Answers

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For more than forty years now, high serum phosphate levels, a highly prevalent condition in patients with chronic kidney disease (CKD), have been associated with the pathogenesis of secondary hyperparathyroidism, a common mineral and bone disorder (MBD).1 Recent epidemiologic and experimental studies have further amplified the role this condition plays in the larger story of CKD-MBD. Experimental studies have demonstrated that high phosphorus plays a key role in the development of vascular calcification2 and impairment of bone mass and strength, induces changes in the expression pattern of muscle and bone-related genes,3,4 and may also act as a pro-aging factor.5 In addition, clinical studies have demonstrated an association among hyperphosphatemia, vascular stiffness, and left ventricular hypertrophy.6 Taking all of the aforementioned findings together, it is reasonable to hypothesize all these untoward actions of phosphorus may ultimately affect mortality, as it has been suggested by several studies carried out in different dialysis cohorts.7,8

The increase in the importance of phosphorus in the spectrum of CKD-MBD also coincides with the description of the multiple actions of a new modulator, fibroblast growth factor 23 (FGF-23). This phosphatonin carries out some effects independent of phosphorus, such as its inhibitory effect on parathyroid hormone synthesis,9 but, so far, most of the biologic actions of FGF-23, including its recently described association with mortality,2,10 seem to be highly interdependent and related to phosphorus, parathyroid hormone, and vitamin D metabolism.11,12

In this issue of JASN, Isakova et al.13 investigate in a prospective cohort of incident hemodialysis patients the hypothesis that therapy with any type of phosphate binder versus no phosphate binder offers survival benefit. To mimic a randomized trial, they used an interesting approach, performing multivariate-adjusted “intention to treat” analysis and multivariate-adjusted “as treated” analysis in which the analyses started at the time the therapy began.

In the intention-to-treat analysis, the phosphate binders group offered a 30% lower mortality compared with the untreated group. The results were less beneficial (18% lower

See related article, “Plasmin in Nephrotic Urine Activates the Epithelial Sodium Channel,” on pages 299–310.

REFERENCES


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