Clues to renal sodium retention

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EXPANSION OF EXTRACELLULAR VOLUME manifests as peripheral and pulmonary edema in chronic heart failure (CHF) patients and can lead to hospitalizations and death (1, 10). Stimulation of the autonomic nervous system, elevated levels of arginine vasopressin (AVP), and activation of the renin-angiotensin-aldosterone systems are thought to contribute to the volume overload associated with this disorder (10, 11, 18, 21, 22). Zheng et al. (31) in an issue of the American Journal of Physiology-Renal Physiology investigate the contribution of the epithelial sodium channel (ENaC) to water and sodium retention seen in a rat model of CHF.

In the aldosterone-sensitive distal nephron, ENaC maintains extracellular volume homeostasis by providing fine control of salt and fluid absorption (3, 23, 27). ENaC-mediated sodium absorption is determined by the electrochemical driving force for sodium, the number of channels present at the plasma membrane, and the open probability of those channels. ENaCs are assembled as trimers composed of three structurally related subunits termed α, β, and γ (8, 14). Zheng et al. (31) present compelling evidence that ENaC dysregulation contributes to sodium retention in CHF. They found that ENaC subunit transcripts and proteins were increased up to twofold, whereas ENaC-mediated sodium absorption was increased about three- to fourfold in CHF rats compared with control rats. Neuroendocrine activation, including elevated levels of plasma AVP, atrial natriuretic factor, and norepinephrine, have been reported in patients with CHF (12). AVP binds to V2 receptors at the basolateral membrane of principal cells in the collecting duct, increasing cellular level of cAMP through the activation of adenylate cyclase (25). cAMP promotes the insertion of an intracellular pool of ENaC in the plasma membrane with a concomitant increase in transepithelial sodium transport (5, 6, 28). It is conceivable that in the absence of a large change in the total pool of channels, elevated levels of systemic AVP may increase the abundance of channels at the apical membrane of CHF rats. Dysregulation of the renin-angiotensin-aldosterone system also has been suggested as a major contributor of sodium retention in CHF, and it may account for the observed difference among ENaC protein expression and ENaC functional activity in the study by Zheng et al. (31). Aldosterone promotes the transcription and translation of ENaC subunit genes and proteins, enhances proteolytic cleavage of the α- and γ-subunits (13), and increases delivery of channels to the plasma membrane (2, 17), which ultimately results in an increase in the number of active channels at the plasma membrane (15, 19). However, the increase in ENaC surface expression only accounts for a minor fraction of the change elicited by the hormone on sodium transport in vivo (13). Proteolytic processing of the ENaC α- and γ-subunits at defined sites within the ectodomain promotes the release of inhibitory peptides with a concomitant increase in the open probability of the channel (4, 9). Noncleaved channels are near electrically silent with an open probability lower than 0.1 (7, 26), channels lacking the inhibitory tract in the α-subunit have an open probability of 0.3–0.4, whereas channels lacking the γ inhibitory tract are almost constitutively open (4, 9). Thus, even with a modest increase in the pool of channels at the plasma membrane, proteolytic cleavage of the α- and γ-subunits could lead to a significant increase in sodium absorption in the aldosterone-sensitive distal nephron. As mentioned above, the functional responses to benzamil were increased three- to fourfold in CHF rats compared with controls, whereas ENaC subunit transcripts and proteins were only increased up to twofold (31). One possible interpretation is that perhaps there are greater amounts of the processed forms of the α- and γ-subunits in the CHF condition. Recent studies have identified a number of proteases that cleave the ENaC α- and γ-subunits and enhance channel activity in heterologous expression systems (16). Enhanced proteolytic activation of ENaC has been implicated in the extracellular volume expansion seen with proteinuric kidney diseases (20, 29) and may have a role in sodium retention seen with CHF.

The sympathetic nervous system has an important role in fluid and sodium handling (11, 21, 22, 30). Diuretic and natriuretic responses to volume expansion are blunted in CHF rats compared with controls, although renal denervation partially reestablishes these responses (22). These results suggested that in addition to the renal nerves, there also might be other factors that are involved in sodium retention during CHF. Zheng et al. (31) now report that renal denervation increases diuresis and natriuresis in rats, even though these parameters were not affected by benzamil (31). The results suggest that ENaC activity is relatively low in rats kept on a normal sodium diet and that renal denervation by itself does not have an effect on basal ENaC activity. Notably, in the setting of CHF, ENaC-mediated sodium absorption was enhanced in denervated rats compared with nondenervated rats. Rates of luminal flow modulate ENaC-mediated sodium absorption and potassium secretion in the cortical collecting duct (24). Although ENaC-mediated sodium absorption is low in rats maintained with a normal sodium diet, in a setting such as CHF, with active channels in the plasma membrane, enhanced distal fluid delivery could produce a further increase in ENaC-mediated sodium absorption.

In conclusion, the article by Zheng et al. (31) provides important insights to sodium and fluid retention in CHF. This study suggests that ENaC contributes to sodium retention and extracellular volume overload seen in CHF patients. Future studies should investigate in more detail the contribution of AVP, the proteolytic processing of the α- and γ-subunits, the
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renin-angiotensin-aldosterone system, and the autonomic nervous system to ENaC-mediated sodium retention in CHF.

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