Amiloride: the “new” renal tonic?

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SODIUM REABSORPTION in the aldosterone-sensitive distal nephron is mediated by the amiloride-sensitive, epithelial sodium channels (ENaC), which are expressed in the apical (luminal) membranes. The regulated reabsorption of sodium at these nephron sites plays a key role in the regulation of extracellular fluid volume and systemic blood pressure (14, 15). The importance of ENaC in these processes is highlighted by functional mutations, both gain-of-function (Liddle’s syndrome) associated with hypertension (17) and loss-of-function (pseudohypoaldosteronism), which is associated with low blood pressure (5). These channels are members of the ENaC/Degenerin family of cation-selective ion channels and are composed of α-, β-, and γ-subunits, which share structural features of two transmembrane domains separated by a large extracellular region and short cytoplasmic amino- and carboxy-terminal tails (3, 4).

The intertwined external loops of the assembled ENaC complex undergo posttranslational modification that plays an important role in activating channels that are expressed in the luminal membrane. A number of proteases have been originally described that were thought to be coexpressed in the apical membrane in close proximity to the ENaC complexes. An increasing number of proteases has been described that cleaves the α or γ ENaC subunits at defined sites in the extracellular domains (6, 7, 16), and this processing may begin in the trans-Golgi network as well as at the apical membrane (26). Prostasin and kallikrein may activate ENaC in the setting of volume depletion and in response to aldosterone (11). In states of increased protein excretion, plasminogen can be filtered and cleaved by soluble urokinase-type plasminogen activator (uPA) to plasmin, which subsequently cleaves and activates ENaC in the apical membrane (9, 10). Soluble plasma uPA and its cognate receptor (uPAR) were previously described as playing a role in tumor progression and metastasis (13), and more recently plasmin has been proposed to play a role in triggering podocyte injury that leads to focal glomerulosclerosis (12).

This mechanism for ENaC activation has been previously proposed as an explanation for the sodium avidity that is characteristic of nephrotic syndrome (20, 21). Over 30 years ago, an off-target inhibitory effect of amiloride was described in micromolar concentrations on the inhibition of uPA (24). This concentration is relevant to inhibition of ENaC in the late distal nephron. Zhang et al. (28) revisited this finding and reported that this off-target effect of amiloride was not seen with triamterene, another ENaC blocker, and was associated with decreased proteinuria, decreased podocyte uPAR expression, and attenuation of glomerulosclerosis. Trimarchi et al. (23) describe a male patient with Fabry syndrome, who continued to have nephrotic range proteinuria despite maximal renin-angiotensin system blockade and enzyme replacement therapy, and showed a striking decrease in urine protein excretion when amiloride was added to his other medications. Fabry disease (22) as well as many other forms of proteinuric kidney diseases (2) are being recognized as fundamentally, or at least initially, as a podocyte disease.

Svenningsen et al. (20) previously reported a tendency to an increased urinary plasminogen/plasmin ratio in nephrotic rats treated with amiloride, and in an issue of the American Journal of Physiology-Renal Physiology they hypothesized that uPA and plasminogen are “aberrantly” filtered in nephrotic syndrome and that amiloride could prevent tubular activation of plasminogen to plasmin by inhibiting uPA. They measured sodium balance, uPA protein and activity, and amiloride concentration in urine from rats with puromycin aminonucleoside-induced nephrotic syndrome (18). Amiloride (2 mg·kg⁻¹·h⁻¹) resulted in urinary concentrations between 10 and 20 μM, with significant reduction in uPA activity, plasminogen activation, protease activity, and sodium retention in this rat model of nephrotic syndrome. In contrast to previous reports (23, 28), total urinary protein was not decreased, which seems to be typical of acute experimental nephrotic models in rodents but not in humans or longer-term rodent models like 5/6th nephrectomy (28).

The current study (18) and other recent papers from this group (1, 19, 27) have emphasized the dual effects of amiloride; directly on ENaC through inhibition of channel blockade and indirectly through its novel effects on uPA activity with consequent attenuation of posttranslational ENaC activation. While these approaches are important for understanding the regulation of ENaC activity in pathologic conditions such as nephrotic syndrome, they do not address the upstream causes of proteinuria and the remarkable “off-target” effects of amiloride that appear to involve the interactions between uPA, its receptor, and β3-integrin that play a critical role in anchoring the podocytes to the glomerular basement membrane (12, 23, 28). Finally, plasmin is a profibrotic molecule that could contribute to scarring and fibrosis in proteinuric states (29). By inhibiting plasmin, amiloride could attenuate scarring and fibrosis in a variety of proteinuric conditions.

The therapeutic window has been opened a bit wider for amiloride; a fresh look is needed to define its unique targets and activities as well as its place among inhibitors of the renin-angiotensin system, mindful of the well-described problems with hyperkalemia (8), and also the previous observations that amiloride can stimulate aldosterone secretion (25), which could attenuate the inhibitory effect of amiloride on ENaC activity.

DISCLOSURES
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REFERENCES


