Improvement of Blood Pressure With Inhibition of the Epithelial Sodium Channel in Blacks With Hypertension

David G. Warnock, P. Darwin Bell

The epithelial sodium channel (ENaC) is a critically important final regulator of the balance between intake and excretion of dietary sodium, and along with the thiazide-sensitive NaCl cotransporter, constitutes the predominant sodium transport systems in the aldosterone-sensitive distal nephron. As proposed by Guyton, and confirmed by the unraveling of the activating ENaC mutations in Liddle’s syndrome, dysregulation of the final balance of sodium intake and excretion can result in chronic volume expansion, plasma renin suppression, and arterial hypertension. 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 relative excess dietary salt intake. The possibility that polymorphisms in the 3 ENaC subunits could contribute to this apparent activation of ENaC and the utility of amiloride as an ENaC blocker in black hypertension have been considered previously.

In this issue of journal, Saha et al describe a systematic investigation of the effects of amiloride, spironolactone, and their use in combination in a short-term, randomized, placebo-controlled crossover study in blacks with established low-renin hypertension. As such, these studies represent important extension of the previous work of this group published in Hypertension. Both agents block the effects of aldosterone on the aldosterone-sensitive distal nephron, with amiloride directly interacting with ENaC and spironolactone affecting all aldosterone-sensitive systems, including ENaC and the thiazide-sensitive NaCl cotransporter. Of note, the 98 black subjects in this report were hypertensive despite their use in combination and therefore decrease the side effect profile of larger doses of either agent. Hyperkalemia is an important limiting side effect, especially if multiple inhibitors of the renin-angiotensin-aldosterone system are used. The possibility that amiloride may directly stimulate renin activation or release could open up new therapeutic possibilities because stimulation of renin activity increases aldosterone secretion, which enhances potassium secretion, whereas the direct effect of amiloride to block ENaC limits potassium secretion. It could useful to tease apart the effects of the amiloride analogues on renin activation to see if they could be distinguished from their direct effects on ENaC.

As pointed out by Saha et al, the synergistic effects of amiloride and spironolactone may permit lower doses of each agent to be used in combination and therefore decrease the side effect profile of larger doses of either agent. Hyperkalemia is an important limiting side effect, especially if multiple inhibitors of the renin-angiotensin-aldosterone system are used. The possibility that amiloride may directly stimulate renin activation or release could open up new therapeutic possibilities because stimulation of renin activity increases aldosterone secretion, which enhances potassium secretion, whereas the direct effect of amiloride to block ENaC limits potassium secretion. It could useful to tease apart the effects of the amiloride analogues on renin activation to see if they could be distinguished from their direct effects on ENaC.

Despite the current enthusiasm for pharmacogenomic approaches and rigorous mathematical descriptions of polygenetic traits such as hypertension, the need for empiric approaches to complex biologic systems remains, and the carefully performed studies by Saha et al provide important insights into the possible role of dysregulation of ENaC in the pathogenesis of low renin hypertension in blacks.
References


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