Small potassium (SK) channels: speculation on a role to regulate aldosterone production and blood pressure

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Key terms
aldosterone; potassium channels; hypertension

In the current issue of Hypertension, Hu et al.\textsuperscript{1} report on the presence of small conductance, calcium (Ca\textsuperscript{++})-activated potassium (K\textsuperscript{+}) channels (SK channels) in a human adrenocortical cell line (H295R). SK channels were also found in normal human adrenals. Using pharmacologic probes, these investigators showed relevance to synthesis of aldosterone: a specific SK channel inhibitor, apamin, increased expression of steroidogenic enzymes and increased both basal and angiotensin II-stimulated aldosterone production. 1-EBIO, an agonist of SK channels, produced opposite effects. The authors suggest that a dysfunctional SK channel could decrease a restraining influence on secretion of aldosterone. Some degree of caution should be applied to the findings. There was a heavy reliance on non-biologic probes and the use of a human cell line (NIH-H295). Although a widely used source of adrenocortical cells, any cell line can lose certain functions over time. Replication by other laboratories will be important.

Produced in the adrenal zona glomerulosa (ZG), aldosterone is a potent sodium (Na\textsuperscript{+})-retaining, K\textsuperscript{+}-secreting hormone. Angiotensin II and K\textsuperscript{+} stimulate its production to, respectively, maintain plasma volume and prevent hyperkalemia\textsuperscript{2}. Both stimuli act by first decreasing a highly polarized membrane potential (angiotensin II by inhibiting K\textsuperscript{+} conductance and extracellular K\textsuperscript{+} by affecting membrane potential directly). The depolarization triggers influx of calcium (Ca\textsuperscript{++}) through voltage-gated channels. The increase in Ca\textsuperscript{++}, serving as second messenger, promotes steroidogenesis. Membrane potential, the intracellular concentration of Ca\textsuperscript{++} and rates of aldosterone synthesis – are all very much dependent on the presence of K\textsuperscript{+} channels.
The movement of $K^+$ ions from inside to outside the cell, along a pathway of declining concentrations, provides a vital contribution to the level of membrane potential (Figure 1-A). Selectivity of the channel for $K^+$ is also essential. This was vividly illustrated in studies of aldosterone producing adrenal adenomas carried out by Chio et al. $^3$ This group identified somatic mutations in the $K^+$ channel KCNJ5. Eight out of 22 tumors had 1 or the other of 2 mutations either within or close by the selectivity filter for $K^+$. There was thus an interference with the normal flow of positive ions to the outside – the reduced selectivity produced instead an inward movement of $Na^+$ ions whose concentration is highest in the extracellular compartment (Figure 1-B). The more positive charge inside the ZG cell would lower membrane potential to where aldosterone production would increase.

An increase in the flow of $K^+$ ions through $K^+$ channels takes place when treating hypertension with certain direct vasodilators such as pinacidil or minoxidil (they are referred to as ‘potassium channel openers’). Their ability to raise membrane potential, to make the cell less positively charged, would be expected to lower aldosterone production, which indeed was shown to occur in the case of pinacidil $^4$. Whether this adds to the antihypertensive properties of these drugs is unclear.

As an aside, it might be noted that SK channels have been studied largely in neuronal tissue in brain. ZG cells have peculiarities to their function that are neurogenic-like. For example, serotonin and beta-adrenergic agents stimulate aldosterone secretion whereas dopamine and atrial natriuretic factor are inhibitory $^2$. Whether SK channels convey to ZG cells this neural element is an interesting consideration.

As the authors point out, variations in SK channels could in some individuals be the basis for primary aldosteronism. On the other hand, a sizable portion of those with hypertension appears to have only a component of excess aldosterone, or at least do not meet the full criteria for having primary aldosteronism. For example, although some patients with resistant hypertension do have primary aldosteronism (~20%), most do not, yet they may still respond amazingly well to administration of an MR antagonist $^5$. When compared to whites, African-Americans appear to have a more expanded volume and on average a lower plasma aldosterone concentration. The BP, however, in comparison to whites, is often more sensitive to a given level of aldosterone $^6$. Finally, those of a more advanced age, the prevailing level of aldosterone may become increasingly capable of raising the BP. Primary aldosteronism is more common in older than in younger individuals, and salt-sensitivity of BP and low-renin states are more commonplace with increases in age $^7$. The aging kidney may lose natriuretic efficiency. In all the patient groups, the levels of aldosterone are typically within the normal range. Nonetheless, they may exceed a threshold wherein additional Na reabsorption mediated by aldosterone leads to a higher BP.

The findings reported on by Hu et al. were generated in the laboratory and have yet to be explored more broadly such as in animal studies or for that matter clinically. Even so, we find it compelling to speculate that variations in $K^+$ channel selectivity could contribute to the underpinnings of these ‘hyperaldosteronism’ types of hypertension. In the end, the extent to which SK channels are shown to influence levels of aldosterone may establish its relevance to blood pressure. Stay tuned.
Acknowledgments

Funded by the National Institutes of Health (RO1-HL095086 and RO-HL 35795) and by a Department of Veterans Affairs Merit Review Award.

References

Aldosterone (Aldo) production and selectivity of K\(^+\) channels for K\(^+\) in zona glomerulosa (ZG) cells. 

**A.** The normal conduction of K\(^+\) ions from a high intracellular concentration to a much lower extracellular concentration. The unidirectional conductance results in a highly polarized negative membrane potential (MP) and a sustained production of Aldo.

**B.** A loss of selectivity for K\(^+\) allows Na\(^+\) to be conducted but in the opposite direction, from its high extracellular concentration to its low intracellular concentration. Na\(^+\) moving from outside to inside the cell reduces MP, increases the concentration of Ca\(^{++}\) which then increases synthesis and secretion of aldosterone.