Renal mineralocorticoid receptor and electrolyte homeostasis

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Terker AS, Ellison DH. Renal mineralocorticoid receptor and electrolyte homeostasis. Am J Physiol Regul Integr Comp Physiol 309: R1068–R1070, 2015. First published July 1, 2015; doi:10.1152/ajpregu.00135.2015.—The renal mineralocorticoid receptor (MR) is a steroid hormone receptor essential for maintaining electrolyte homeostasis. Its role in mediating effects of aldosterone was likely vital in enabling the evolution of terrestrial life. Dysregulated aldosterone-MR signaling has been identified as the cause of multiple clinical diseases, suggesting the physiological importance of the MR. While the physiology of this pathway has been studied for over 60 years, only more recently have genetic mouse models been available to dissect its function in vivo. This review will focus on recent advances in our knowledge of MR function with an emphasis on these models.

mineralocorticoid; Na⁺ Cl⁻ cotransporter; homeostasis; potassium; sodium

THE MINERALOCORTICOID RECEPTOR (MR) is essential for blood pressure regulation and electrolyte homeostasis. Physiologically, the MR mediates effects of the hormone aldosterone on electrolyte balance, promoting Na⁺ retention and K⁺ excretion. The evolution of the aldosterone-MR relationship likely occurred in response to dramatic changes in ionic stress experienced when organisms transitioned from aquatic to terrestrial life. In the ocean, aquatic organisms had the burden of fighting constant salt loading, whereas the prospect of a terrestrial existence presented the opposite problem, preventing their emergence from the sea. As the ability to synthesize aldosterone first appeared in tetrapods (3), the aldosterone-MR axis was likely part of the solution to maintain ion balance during this transition from water to land. The physiological importance of the MR and aldosterone is supported by the numerous clinical syndromes caused by dysregulated MR signaling [e.g., Addison’s disease, primary aldosteronism, Liddle syndrome (17), and pseudohypoaldosteronism type I (PHA I) (4)].

The MR is expressed in multiple tissues and has physiological functions throughout the body (12), but it mediates aldosterone effects on ion homeostasis predominantly through activity in the kidney (16). Furthermore, while the MR is expressed along most of the nephron, aldosterone signaling occurs mainly along the aldosterone-sensitive distal nephron (ASDN) (16), which includes the connecting tubule (CNT), collecting duct (CD), and perhaps part of the late distal convoluted tubule (DCT). Specific localization of aldosterone effects along the nephron is related to ASDN-specific expression of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) (2, 9, 11, 18, 25), which converts cortisol to cortisone. Both cortisol and aldosterone can activate the MR and they have equal affinities for the receptor. Because cortisol circulates at 1,000 times the concentration of aldosterone, in most cells, cortisol outcompetes aldosterone for MR binding; however, in the ASDN, aldosterone effects are unmasked by 11β-HSD2 (6).

The essential transport elements of the ASDN are now established and include the basolateral Na-K-ATPase, which moves 3 Na⁺ out of the cell in exchange for 2 K⁺ in, keeping the intracellular [Na⁺] low. At the apical membrane, the epithelial Na⁺ channel (ENaC) mediates Na⁺ entry, down its electrochemical gradient. It lies in parallel with the renal outer medullary K⁺ channel (ROMK). When plasma [K⁺] rises, the cells in the ASDN respond by increasing K⁺ secretion, even if plasma aldosterone is kept constant. A rise in peritubular [K⁺] directly stimulates the Na-K-ATPase, as well as ENaC and ROMK, all of which favor K⁺ secretion (7). Aldosterone amplifies this response, as its secretion is also stimulated by rises in plasma [K⁺]. As a steroid hormone, aldosterone binds the MR in the cytosol, followed by translocation to the nucleus where the complex functions as a transcription factor. While there are many aldosterone-sensitive genes, most textbooks describe ENaC as the canonical final common pathway of aldosterone-MR signaling in the CNT/CD (5). Mechanistic details are complicated, but ultimate effects include increased ENaC transcription, apical abundance, and open probability (13). Increased ENaC activity increases Na⁺ reabsorption and the magnitude of the negative lumen potential, further enhancing K⁺ secretion through apical K⁺ channels (10).

More recently, aldosterone has been shown to regulate the thiazide-sensitive Na⁺ Cl⁻ cotransporter (NCC). While aldosterone infusion increases (8, 23), and its absence reduces (21), NCC abundance and activity in animals, several observations...
raise questions as to whether the DCT MR mediates these effects. First, Liddle syndrome and PHA I, which are caused by disrupted ENaC function, phenocopy hyper- and hypoaldosterone states, suggesting the physiological effects of aldosterone are predominantly due to effects on ENaC and not NCC. Second, it has recently been observed that changes in plasma [K+] affect NCC abundance and function (20). As dysregulated aldosterone signaling almost always affects plasma [K+], via effects on the CNT/CD, observed NCC changes in hyper- and hypoaldosterone states may be secondary to plasma [K+] disturbances.

Over the last two decades, several mouse models have been developed to elucidate the role of aldosterone-MR signaling in vivo. These models have been instrumental in demonstrating the importance of the MR in vivo. The first of these models, developed by Schütz and colleagues (1), employed constitutive, total-body MR deletion. While not embryonic lethal, these animals died within the first 2 wk of life and displayed Na+ wasting and K+ retention. To determine whether the severe phenotype was due to loss of MR function in the CNT and CD, Berger and colleagues deleted the MR in principal cells, both constitutively (14), and in an inducible manner (15), using the aquaporin-2 promoter. Both of Berger’s CNT/CD models displayed relatively mild phenotypes at baseline. Na+ wasting and increased urine volume only became apparent during Na+ restriction; on a normal diet, the mice appeared relatively normal. Because these mice did not phenocopy the effects of total body MR deletion, the authors suggested that MR effects in segments other than the CNT and CD likely explain differences between the models.

To determine whether the different phenotypes after total body deletion and CNT/CD deletion were due to MR effects along other nephron segments, we have recently deleted the MR along the entire nephron, in an inducible fashion, using the Pax8/LC1 CRE/Lox system (19). After MR deletion with doxycycline, the kidney-specific (KS) MR−/− animals survived but demonstrated weight loss, Na+ wasting, elevated plasma [K+], and reduced blood pressure, even on a normal Na+ and K+ diet. Additionally, they had reduced abundance of NCC, phosphorylated NCC (pNCC, the activate form), and total αENaC. While β and total γENaC levels remained unchanged, abundance of the cleaved form of γENaC was greatly reduced. Stress with either a low Na+ or high K+ diet greatly exacerbated the weight loss, Na+ wasting, and hyperkalemia experienced by the KS MR−/− mice. Furthermore, both of these dietary manipulations dramatically reduced pNCC abundance, had no effect on α or γENaC, and increased βENaC abundance compared with baseline in the KS MR−/− mice.

These data suggest that the MR is required for αENaC synthesis and γENaC cleavage, but not for synthesis of the β subunit. βENaC abundance is likely increased following treatment with low-Na+ and high-K+ diets because MR-independent regulation. Regarding NCC, data are not only consistent with a direct role for MR in the DCT in regulating NCC, but also with effects on NCC being secondary to elevated plasma [K+]. To determine whether aldosterone affects NCC independent of altered plasma [K+], we next showed that aldosterone-infused wild-type animals had elevated NCC and pNCC abundance and reduced plasma [K+]. Consumption of a high-K+ diet prevented effects of aldosterone infusion on both plasma [K+] and NCC, suggesting that aldosterone infusion is not sufficient to affect NCC and changes are likely due to reduced plasma [K+].

K+ disturbances are becoming more widely accepted as dominant forces on NCC activity (20, 22, 24). Observations described herein provide evidence that aldosterone effects on NCC in disease models are predominantly secondary to changes in plasma [K+] and not direct effects on the MR in NCC-expressing cells (Fig. 1). If true, this would suggest that altered NCC activity in (pseudo-) hyper- and (pseudo-) hypoaldosterone states are homeostatic with respect to K+ balance at the expense of Na+ balance.

For example, in PHA I, reduced ENaC activity promotes Na+ wasting and K+ retention. If Na+ were the dominant force on NCC, one would expect its activity to increase secondary to elevated circulating angiotensin II, and perhaps aldosterone, levels. However, with K+ dictating NCC function, its activity is likely reduced to promote distal Na+ flow in an attempt to drive ENaC-mediated K+ secretion. Unfortunately, ENaC function is impaired and this exacerbates Na+ wasting without ameliorating the hyperkalemia. This may explain the profound Na+ wasting seen in PHA I patients that appears disproportionate to the 2–3% of the filtered Na+ load normally reabsorbed by ENaC. If NCC is also turned off, patients may be wasting closer to 15% of the filtered Na+ load, causing the severe phenotype.

While this has yet to be shown in human disease, animal models support this hypothesis. Specifically, amiloride-treated mice had greatly reduced NCC abundance, an effect that was negated by maintaining plasma [K+] in the normal range with a low-K+ diet (20). A similar line of logic would apply to a hypoaldosterone state, such as Addison’s disease, and the
opposite scenario would occur in Liddle syndrome or primary hyperaldosteronism. Details remain to be worked out, and it could be that both the DCT MR and plasma \( K^+ \) are able to affect NCC by their own independent mechanisms in vivo. A DCT-specific MR knockout mouse model could elegantly address this, but unfortunately, it has been technically difficult to generate such a model. Also remaining unanswered is why the total body MR knockout mouse dies so early in life. It seems likely that it is either because the renal MR is essential in the perinatal period, or because extrarenal MR is required for life, either perinatally or in adulthood. Just as the genetic mouse models described have enhanced our understanding of the MR, perhaps future ones can provide answers to these questions.

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**REFERENCES**


