Adult nephron-specific MR-deficient mice develop a severe renal PHA-1 phenotype

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Aldosterone is the main mineralocorticoid hormone controlling sodium balance, fluid homeostasis, and blood pressure by regulating sodium reabsorption in the aldosterone-sensitive distal nephron (ASDN). Germline loss-of-function mutations of the mineralocorticoid receptor (MR) in humans and in mice lead to the ”renal” form of type 1 pseudohypoaldosteronism (PHA-1), a case of aldosterone resistance characterized by salt wasting, dehydration, failure to thrive, hyperkalemia, and metabolic acidosis. To investigate the importance of MR in adult epithelial cells, we generated nephron-specific MR knockout mice (MR(Pax8/LC1)) using a doxycycline-inducible system. Under standard diet, MR(Pax8/LC1) mice exhibit inability to gain weight and significant weight loss compared to control mice. Interestingly, despite failure to thrive, MR(Pax8/LC1) mice survive but develop a severe PHA-1 phenotype with higher urinary Na(+) levels, decreased plasma Na(+), hyperkalemia, and higher levels of plasma aldosterone. This phenotype further worsens and becomes lethal under a sodium-deficient diet. Na(+)/Cl(-) co-transporter (NCC) protein expression and its phosphorylated form are downregulated in the MR(Pax8/LC1) knockouts, as well as the αENaC protein expression level, whereas the expression of glucocorticoid receptor (GR) is increased. A diet rich in Na(+) and low in K(+) does not restore plasma aldosterone to control levels but is sufficient to restore body weight, plasma, and urinary electrolytes. In conclusion, MR deletion along the nephron fully recapitulates the features of severe human PHA-1. ENaC protein expression is dependent on MR activity. Suppression of NCC under hyperkalemia predominates in a hypovolemic state.
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