SIGNIFICANCE STATEMENT

Systemic pseudohypoaldosteronism type 1 is a life-threatening disease caused by mutations in either the α, β, or γ subunit of the amiloride-sensitive epithelial sodium channel (ENaC). It is characterized by weight and salt loss, metabolic acidosis, dehydration, hyponatremia, and hyperkalemia. Patients are commonly treated with salt supplementation. Using inducible, nephron-specific γENaC knockout mice, this work demonstrates that the prevention of hyperkalemia is required for survival. Thereby, the plasma potassium concentration becomes determining for the activity of the thiazide-sensitive sodium chloride cotransporter. This may also explain why human mutations within the γENaC subunit are relatively rare. The understanding of this functional link may provide insight into the pathogenesis of systemic pseudohypoaldosteronism type 1 and optimize the treatment of patients.