

SIGNIFICANCE STATEMENT

Nedd4-2 associates with the epithelial Na⁺ channel (ENaC), resulting in its ubiquitylation and then, internalization and degradation. In the absence of *Nedd4-2*, increased renal Na⁺ absorption and increased BP are observed. Despite high levels of *Nedd4-2* expression in intercalated cells, the role that these cells play in the changes in BP observed with *Nedd4-2* gene ablation is unknown. This study is the first to show that *Nedd4-2*-dependent changes in BP occur in part from *Nedd4-2* expressed in intercalated cells. Moreover, this study shows that *Nedd4-2* gene ablation within intercalated cells stimulates electroneutral apical Cl⁻/HCO₃⁻ exchange in mouse CCD, in part by upregulating pendrin.