SIGNIFICANCE STATEMENT

Fibroblast growth factor–23 (FGF-23) regulates mineral homeostasis by activating FGF receptor (FGFR)/α-Klotho complexes to control phosphate reabsorption in the proximal tubule and calcium absorption in the distal nephron. Several recent studies point to broader FGF-23–dependent renal actions that secondarily regulate cardiovascular homeostasis. The gene encoding the type 1 FGFR (FGFR1) was deleted selectively in the distal tubule segments of mice using CRE-Lox technology. Loss-of-FGFR1 function resulted in hypertension and cardiomegaly in association with increased renal expression of the bumetanide-sensitive Na-K-2Cl transporter and decreased expression of α-Klotho. These effects are opposite to those predicted by FGF-23 activation of FGFR/α-Klotho complexes in the kidney and point to FGFR1 as a novel target for treating hypertension.