SIGNIFICANCE STATEMENT

Diabetes and obesity are leading causes of kidney and cardiovascular disease. Previous data implicate nuclear hormone receptors activated by bile acids, the farnesoid X receptor (FXR) and the Takeda G-protein-coupled receptor (TGR5). The present studies demonstrate that treatment of mice with type 1 diabetes, type 2 diabetes, or diet induced obesity with a dual FXR and TGR5 agonist improved proteinuria and prevented podocyte injury, enhanced mitochondrial function, inhibited ER stress, and improved renal fatty acid and cholesterol metabolism. These results demonstrate novel signaling pathways for FXR and TGR5 in the kidney and suggest they are promising targets for treatment of kidney disease in diabetes and obesity.