SIGNIFICANCE STATEMENT

Defective reabsorption of filtered molecules by endocytosis in the kidney proximal convoluted tubule (PCT) occurs in numerous diseases, and endocytosis is also an important entry route for nephrotoxic substances. PCT cells have a highly developed endolysosomal system (ELS), but relatively little is known about its function *in vivo*. The authors measured ELS protein expression and used advanced imaging techniques to demonstrate that early and late PCT segments show striking differences in ligand uptake and ELS function. They found that the early segment is highly specialized to perform protein reabsorption *via* receptor-mediated endocytosis, whereas nonspecific fluid phase endocytosis occurs along the entire PCT. These findings have important implications for understanding PCT function, topographic patterns of renal disease, and the origins of tubular proteinuria.