SIGNIFICANCE STATEMENT

Acidosis is an important complication of AKI and CKD. Renal intercalated cells (ICs) are major players in acid-base homeostasis *via* the proton pump, V-ATPase. V-ATPase activity is regulated by vesicle recycling, and cAMP induces its apical membrane accumulation. Adenosine increases cAMP in other cell types, but its effect on IC function is unknown. This study shows that adenosine stimulates V-ATPase–dependent proton secretion *via* the cAMP/PKA pathway through apical adenosine receptors in medullary ICs. Our results reveal a novel mechanism by which ICs respond to luminal agonists and provide a new biologic framework for a better understanding of the effect of adenosine-targeted therapeutics on kidney function.