Multicopy Crystallographic & Biophysical Analyses of the N-terminal Domain of NBCe1-A: Illumination of the Human R298S Mutational Defect

Harry S. Gill*, Ali Ramezani, Talal Alzahrani, Dominic Raj

The George Washington University & The GW Medical Faculty Associates, Department of Medicine, Division of Renal Diseases & Hypertension 2300 I St, NW, Ross Hall 436B, Washington, DC 20052 Tel: 202-994-4587

INTRODUCTION

Background: The sodium-HCO3-exchanger NBCe1-A is responsible for the acid-base homeostasis in the body, and mutations in the gene encoding NBCe1-A (SLC4A4) cause permanent isolated proximal renal tubular acidosis (pRTAA) and eye abnormalities. While the N-terminal (NT) domain of NBCe1-A is responsible for the pH-dependent activity of NBCe1-A, its function is not clear. The aim of this study was to investigate the biochemical properties of the NT domain of NBCe1-A.

METHODS

The NT domain of NBCe1-A was expressed in mammalian cells and purified. The pH-dependent activity of NBCe1-A and its NT domain was studied by measuring pH changes induced by NBCe1-A and its NT domain over time in a bicarbonate-loaded cell assay. The pH dependence of the NT domain was studied by measuring pH changes induced by the NT domain at different pH values. The pH-dependent activity of NBCe1-A and its NT domain was also studied by measuring pH changes induced by the NT domain in a bicarbonate-loaded cell assay.

RESULTS

The NT domain of NBCe1-A is pH-dependent and is responsible for the pH-dependent activity of NBCe1-A. The NT domain is activated at low pH and inhibited at high pH. The pH dependence of the NT domain is due to the presence of a conserved histidine residue that acts as a pH sensor.

CONCLUSIONS

The NT domain of NBCe1-A is pH-dependent and is responsible for the pH-dependent activity of NBCe1-A. The NT domain is activated at low pH and inhibited at high pH. The pH dependence of the NT domain is due to the presence of a conserved histidine residue that acts as a pH sensor.