Conserved Charged Amino Acid Residues in the Extracellular Region of Sodium/Iodide Symporter are Critical for Iodide Transport Activity

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Background: Sodium/iodide symporter (NIS) mediates the active transport and accumulation of iodide from the blood into the thyroid gland. His-226 located in the extracellular region of NIS has been demonstrated to be critical for iodide transport in our previous study. The conserved charged amino acid residues in the extracellular region of NIS were therefore characterized in this study.

Methods: Fourteen charged residues (Arg-9, Glu-79, Arg-82, Lys-86, Asp-163, His-226, Arg-228, Asp-233, Asp-237, Arg-239, Arg-241, Asp-311, Asp-322, and Asp-331) were replaced by alanine. Iodide uptake abilities of mutants were evaluated by steady-state and kinetic analysis. The three-dimensional comparative protein structure of NIS was further modeled using sodium/glucose transporter as the reference protein.

Results: All the NIS mutants were expressed normally in the cells and targeted correctly to the plasma membrane. However, these mutants, except R9A, displayed severe defects on the iodide uptake. Further kinetic analysis revealed that mutations at conserved positively charged amino acid residues in the extracellular region of NIS led to decrease NIS-mediated iodide uptake activity by reducing the maximal rate of iodide transport, while mutations at conserved negatively charged residues led to decrease iodide transport by increasing dissociation between NIS mutants and iodide.

Conclusions: This is the first report characterizing thoroughly the functional significance of conserved charged amino acid residues in the extracellular region of NIS. Our data suggested that conserved charged amino acid residues, except Arg-9, in the extracellular region of NIS were critical for iodide transport.