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The Sodium/Iodide Symporter (NIS): An Unending Source of Surprises

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The Na^+/I^- symporter (NIS) is a key plasma membrane protein that mediates active I^- transport in the thyroid and such other tissues as salivary glands, stomach, intestine, choroid plexus, and lactating breast. Our group isolated the cDNA encoding NIS in 1996 and we have since characterized it extensively. Even before the molecular identification of NIS, its activity was known and used for over 60 years in the diagnosis and treatment of thyroid disease with radioiodide.

NIS-mediated I^- uptake is the first step in thyroid hormone biosynthesis. NIS mediates the inward simultaneous movement of Na^+ and I^- with a 2:1 stoichiometry, thus resulting in a net transfer of positive charge into the cell (i.e., electrogenic transport). We recently reported that NIS translocates different anion substrates with different stoichiometries, as Na^+/perchlorate (or perrhenate) transport is electroneutral. Valuable mechanistic information on NIS has been obtained by the characterization of NIS mutants that cause congenital I^- transport defect in patients. Here we provide a detailed study of the G93R NIS mutant. We show that the presence of a positive charge at position 93 does not cause the protein's lack of activity. As we substituted neutral amino acids at this position, we observed that the longer the side chain of the substituted residue, the lower the protein's activity. G93T and G93N NIS exhibited significantly higher K_m values for I^- than WT NIS, the first time that such a change has been observed in any NIS mutants. Strikingly, we show by kinetic analysis that G93T-mediated Na^+/perrhenate symport is electrogenic with a 2:1 stoichiometry, a discovery confirmed by the detection of currents elicited by perrhenate (or perchlorate) in G93T NIS–expressing *X. laevis* oocytes in electrophysiological experiments. These observations demonstrate that a single amino acid substitution at position 93 converts NIS-mediated Na^+/perchlorate (or perrhenate) transport stoichiometry from electroneutral to electrogenic. Based on the 3-D structure of the bacterial Na^+/galactose transporter, we built a 3-D homology model of NIS and we propose a mechanism in which changes from an outwardly open to an inwardly open conformation during the transport cycle use G93 as a pivot.

After our cloning of NIS, several groups have used it in gene transfer studies to express it in tissues that otherwise do not express it endogenously, thus rendering susceptible to radioiodide treatment. In contrast, NIS is endogenously expressed in breast cancer and its metastases. The implications of these strategies will be discussed.