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Steady-state Function of the Ubiquitous Mammalian Na/H Exchanger (NHE1) in Relation to Dimer Coupling Models with 2Na/2H Stoichiometry

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We wish to acknowledge that, in our recent article about Na/H exchange function in fibroblasts, we overlooked a previous modeling effort by Dr. Alan M. Weinstein (Weinstein, A.M. 1995. *J. Gen. Physiol.* 105:617–641) that focused on a dataset for NHE function in microvillus membrane vesicles (i.e., NHE3) by Aronson et al. (Aronson, P.S., M.A. Suhm, and J. Nee. 1983. *J. Biol. Chem.* 258:6767–6771). Data in this article documents that higher rates of Na extrusion can be activated in these vesicles by extravesicular Na (i.e., via Na/Na exchange) than by extravesicular protons under otherwise identical conditions. As modeled by Weinstein, Na transport must be assumed to occur at 3.3-fold greater rates than proton transport to account for the dataset. We have verified this interpretation, as described in Supplement to the Correction Figure 1: A simple consecutive transport model can account very well for the data of Aronson et al., whereby the best fits using a threefold greater Na translocation rate give dissociation constants for protons and Na of 43 nM and 18.6 mM, respectively. We find that still larger Na translocation rates (up to 10-fold greater) allow still somewhat better data fits. We stress that the success of simple transport models with this dataset does not modify in any way our conclusions from the proton flux measurements described in our article. We tested extensively whether "unequal transport rates" might improve simulations of our data. Neither this modification nor any of many other modifications tested allow simple models to account for the major complexities discussed in detail in our article: (1) "steep" extracellular Na dependencies with low cytoplasmic proton concentrations in forward mode and steep cytoplasmic Na dependencies in reverse mode, (2) apparent decreases of proton dissociation constants with increasing cis Na concentrations, and (3) "biphasic" concentration dependencies of both protons and Na in different circumstances that depend on the concentrations of trans ions. Furthermore, we find that our models account qualitatively very well for the data on NHE3 in the article by Aronson et al. when the Na translocation rates are increased with respect to the proton translocation rates, and with adjustment of the ion affinities, the fits can be quantitatively accurate. Results for the "serial" model with strict 2Na/2H exchange are given in Supplement to the Correction Figure 2, whereby only the Na translocation rates were changed from the published parameters, namely by increasing them by a factor of 3.

We apologize for our failure to note this previous work, and we express additional gratitude to Dr. Weinstein for alerting us to two errors in the equations published in our article: First, in Eq. 14, Na flux occurring via the 2Na/2H exchange mode must be multiplied by 2, as follows, to reflect the stoichiometry:

$$Rnhe = K_{trans} \cdot 2 \cdot (1\text{-}F_{Mode1}) \cdot (E2_{Mode2} \cdot Fno^2\text{-}E1_{Mode2} \cdot Fni^2) + K_{trans} \cdot F_{Mode1} \cdot (E2_{Mode1} \cdot Fno\text{-}E1_{Mode1} \cdot Fni). \quad (14)$$

Accordingly, the published simulations reflect a 2Na/2H exchange mode that operates 50% slower than the 1Na/1H exchange mode. Second, two division symbols were inadvertently inserted into Eq. 15 in the final manuscript. The correct equation, which was used in the simulations presented, is:

$$D_{out} = 1 + (Na_o/K_N) \cdot (1+Na_o/K_N+H_o/K_H) + (H_o/K_H) \cdot (1+H_o/K_H+Na_o/K_N). \quad (15)$$

The Supplement to the Correction is available at http://www.jgp.org/cgi/content/full/jgp.200810016021309c/DC1.