Na^+/H^+ Exchanger

Transporter

In Mitochondria

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Function

The Na^+, which enters the matrix in exchange of Ca^{2+} via the NCE, is extruded from the matrix in exchange of H^+ via the NHE. The function of the NHE is to maintain a low $[Na^+]$ (2–5 mM) in respiring mitochondria to favor the influx of Na^+ and efflux of Ca^{2+} via the NCE.

Mechanism

Mitochondrial NHE is electroneutral, and hence the flux through the NHE does not depend on the membrane potential $\Delta\Psi$. However, the activity of the NHE is inhibited by alkaline matrix pH.

The kinetic model of the NHE is based on a reversible, rapid-equilibrium, random-order bi-bi kinetic mechanism for the binding of Na^+ and H^+ to the NHE. Thus, the NHE model is similar to the Na^+/Ca^{2+} exchanger model, except that the NHE model takes into account the inhibitory effects by the alkaline matrix pH, as well as the simplifying assumption that $K_{H,NHE} << K_{Na,NHE}$.

Equations

The NHE flux expression is given by

$$J_{NHE} = \frac{X_{NHE}[H^+]_x^{\,2}}{Ki_{H,NHE}(Ki_{H,NHE}+[H^+]_x)}\left(\frac{[H^+]_e[Na^+]_x - [H^+]_x[Na^+]_e}{K_{Na,NHE}([H^+]_e+[H^+]_x)+[H^+]_e[Na^+]_x+[H^+]_x[Na^+]_e}\right)$$

where

$$Ki_{H,NHE} = 10^{-7}\ \mathrm{M}\cdot$$

X_{NHE} (mol mg^{-1} s^{-1}) is the NHE activity and $K_{Na,NaH}$ (M) is the Michaelis-Menten constant for the binding of Na^+ to the NHE. The factor $X_{NHE}\cdot[H^+]_x^{\,2}/(Ki_{H,NHE}\cdot(Ki_{H,NHE}+[H^+]_x))$ with $Ki_{H,NHE} = 10^{-7}$ M represents the inhibition of the NHE by alkaline matrix pH ($pH_x > 7$).

Parameters

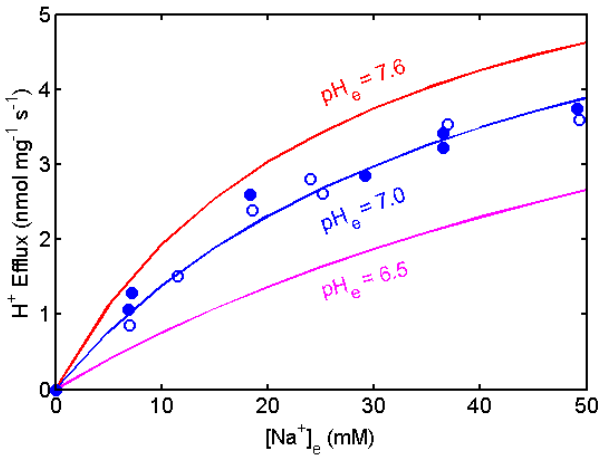
The two free parameters X_{NHE} and $K_{Na,NaH}$ are characterized here based on published experimental data on initial (pseudo-steady) flux rates via the NHE with varying levels of external buffer pH, matrix pH, and external Na^+ in purified mitochondria from rat heart and rat liver.

Table 1: Parameter values for the NHE model (activities in mmol/mg/s can be converted to mmol/l/s by using the conversion factor 1 mg mitochondrial protein = 3.67 µl mitochondria); MM stands for Michaelis-Menten.

Parameter	Description	Values	Units	Reference
$K_{Na,NHE}$	MM binding constant of Na^+ for the Na^+/H^+ exchanger	22.0 (rat heart/liver)	mM	[1,2]
$Ki_{H,NHE}$	Inhibition constant for matrix H^+ for the Na^+/H^+ exchanger	$10^{-7.0}$ (rat heart/liver)	M	[1,2]
X_{NHE}	Na^+/H^+ exchanger activity	12.0 (rat heart/liver)	nmol/mg/s	[1,2]
		18.0 (rat heart)	nmol/mg/s	[1,2]

Fits to Data

A



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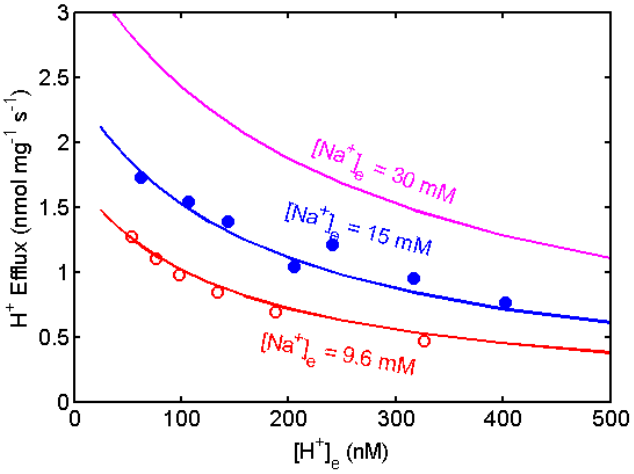

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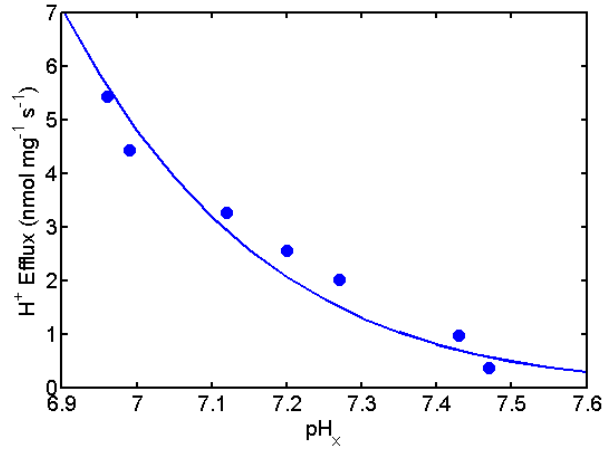

D

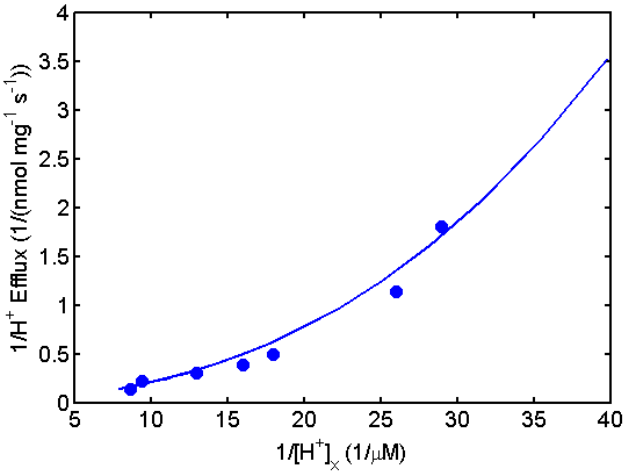

Figure 1: Fitting of NHE model (lines) to data (points) on NHE fluxes. The initial rates of H^+ efflux or Na^+ influx were measured (A) with varying external buffer [Na^+] and fixed external buffer pH = 7.0 and matrix pH = 6.95 in purified mitochondria from rat heart (the solid circles are the measured H^+ efflux rates while the open circles are the calculated H^+ efflux rates from the measured rates of decreased matrix pH with a fixed matrix buffering capacity of 36 nmol H^+/mg/pH unit) [1], and (B) with varying external buffer pH and fixed external buffer [Na^+] = 9.6 mM and 15 mM and matrix pH = 7.0 in purified mitochondria from rat liver [2]. The model fits to these data sets with $K_{Na,NHE}$ = 22 mM and X_{NHE} = 12 nmol/mg/s (for both Na^+ influx and H^+ efflux). (C,D) The fitting of the same kinetic model to another data set is shown where the initial rates of decrease in matrix pH or H^+ efflux in rat heart mitochondria were measured with varying matrix pH and fixed external buffer pH = 7.0 and [Na^+] = 50 mM [1]. For the kinetic model to fit this data set, the X_{NHE} value is adjusted to 18 nmol/mg/s while keeping the $K_{Na,NHE}$ value fixed at 22 mM.

References

1. Kapus A, Ligeti E & Fonyo A. (1989). Na^+/H^+ exchange in mitochondria as monitored by BCECF fluorescence. *FEBS Lett* **251,** 49-52.

2. Kapus A, Lukacs GL, Cragoe EJ, Jr., Ligeti E & Fonyo A. (1988). Characterization of the mitochondrial Na^+-H^+ exchange. The effect of amiloride analogues. *Biochim Biophys Acta* **944,** 383-390.