

Theoretical Effects of Transmembrane Electroneutral Exchange on Membrane Potential

RON JACOB, DAVID PIWNICA-WORMS, C. RUSSELL HORRES,
and MELVYN LIEBERMAN

From the Department of Physiology, Duke University Medical Center, Durham, North Carolina 27710

ABSTRACT Transmembrane electroneutral transport mechanisms [e.g., Na/H exchange, Cl/HCO₃ exchange, (K + Cl) cotransport] have recently been identified in a wide variety of cell types. If these exchanges sum to give a net electroneutral Na/K exchange, they may hyperpolarize the membrane potential beyond the value calculated from the Mullins-Noda equation, provided the cell maintains steady state intracellular ionic concentrations. In extreme circumstances, the membrane potential could hyperpolarize beyond the potassium reversal potential. This effect is mediated by the electrogenic Na/K pump. If either Na or K exchanges electroneutrally against a third ion (e.g., Na/Ca exchange), then the exchange may depolarize the membrane potential.

INTRODUCTION

Electroneutral transport is usually assumed not to contribute to the membrane potential (E_m), although E_m can be affected by direct interaction within the membrane between an electroneutral process and an electrodiffusive pathway (Schwartz, 1971). We will show that, for a cell in steady state and in the absence of any such interaction within the membrane, the magnitude of an electroneutral exchange can affect E_m even to the extent, in extreme circumstances, of driving E_m beyond the most negative ionic equilibrium potential (usually E_K).

Of the various equations for E_m , the most widely used, the Goldman, Hodgkin, Katz (GHK) equation (Goldman, 1943; Hodgkin and Katz, 1949), was originally derived by assuming a constant electric field across the membrane and equating the sum of the passive ionic currents to zero. The derivation only requires constant fluxes (flux steady state) so that, when applied to a membrane enclosing a cell, the intracellular concentrations may be changing. Indeed, because no allowance is made for active transport, there must be a net flux of each permeant ion across the membrane. Thus, the equation does not strictly apply to living cells, which have constant intracellular concentrations (concentration steady state).

Address reprint requests to Dr. Ron Jacob, Dept. of Physiology, Box 3709, Duke University Medical Center, Durham, NC 27710.

MODIFICATIONS OF THE GHK EQUATION

Active Na/K Transport

The constant field requirement has been relaxed in a variety of ways (Schultz, 1980) to make the GHK equation more generally applicable to membranes with no active transport. To accommodate active transport, the GHK equation has been modified in two different ways. Moreton (1969) included the absolute fluxes caused by the pump using the same zero net current constraint as used in deriving the GHK equation. Mullins and Noda (1963), on the other hand, derived a steady state equation, which included the Na/K coupling ratio (stoichiometry) of the pump and not the magnitude of the pump fluxes.

Mullins-Noda Equation

To derive the Mullins-Noda (MN) equation, the sum of the fluxes across the membrane is equated to zero for each ionic species so that passive diffusion is balanced by active transport and there is no net transmembrane movement of ions. The equation describes a concentration steady state and the constraints necessarily imply that the net transmembrane current is zero. Considering a simple case where the membrane is permeable only to K and Na (as is often assumed, for example, in nerve [Hille, 1977] and resting cardiac muscle [Spere-lakis, 1979]) and the gradients for these ions are maintained by an active Na/K pump, the MN equation reads

$$E_m = \frac{RT}{F} \ln \left[\frac{r \cdot P_K \cdot K_o + P_{Na} \cdot Na_o}{r \cdot P_K \cdot K_i + P_{Na} \cdot Na_i} \right],$$

where K_o and K_i are extra- and intracellular potassium concentrations, Na_o and Na_i are extra- and intracellular sodium concentrations, P_K and P_{Na} are potassium and sodium permeabilities, r is the Na/K pump stoichiometry,¹ and R , F , and T have their usual meaning. Assuming reasonable values for the concentrations and calculating E_m for varying P_{Na}/P_K shows that the difference in membrane potential between a cell with an electroneutral and an electrogenic Na/K pump (with $r = 3/2$) will not be much greater than 10 mV: this pump contribution is maximum when $P_{Na} \approx P_K$ and cannot hyperpolarize the membrane beyond E_K in the steady state (see also Ascher, as referred to in Thomas, 1972).

The dominant constraint in deriving the MN equation is the Na/K pump stoichiometry (r): the membrane must seek a potential, defined by the equation, where the passive sodium and potassium fluxes (j_{Na} and j_K) flow in the same ratio as the active fluxes (m_{Na} and m_K) so that the passive fluxes can be balanced by the Na/K pump. With one-to-one pump stoichiometry ($r = 1$), the MN equation formally reduces to the GHK equation because $j_{Na}/j_K = -1$ (or $j_{Na} + j_K = 0$), which is the constraint used to derive the GHK equation. However, the GHK equation is not a special case of the MN equation because the GHK equation applies only to a flux steady state, whereas the MN equation with $r = 1$ applies to a concentration steady state.

¹ We assume that the Na/K pump has a fixed stoichiometry and is unable to respond to changing conditions by varying its stoichiometry ("slippage").

Electroneutral Na/K Exchange

Evidence from several cell systems suggests the existence of various exchangers and cotransporters that appear to be electroneutral. These include Na/H exchange (Roos and Boron, 1981; Piwnica-Worms and Lieberman, 1983), Cl/HCO₃ exchange (for review, see Lowe and Lambert, 1983), and (K + Cl) cotransport (for review, see Hoffman, 1982) (Fig. 1a), which may act in unison in a variety of physiological phenomena including pH_i regulation (Roos and Boron, 1981; Nuccitelli and Deamer, 1982) and changes in cell volume (Lowe and Lambert, 1983; Cala, 1980). In the steady state, the net effect of these exchange mechanisms could be an electroneutral Na/K exchange (Fig. 1b): for

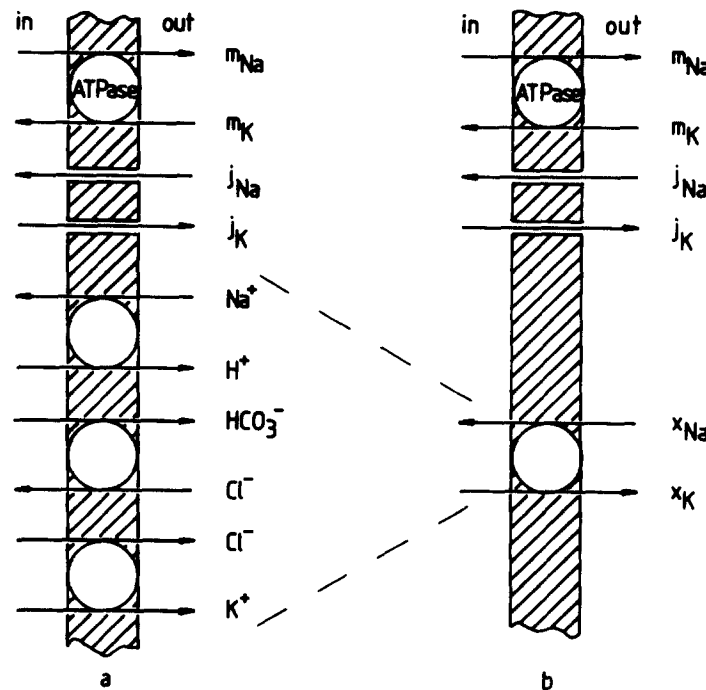


FIGURE 1. (a) Schematic for a membrane containing an Na/K pump, electrodiffusive pathways for Na and K, and various electroneutral exchangers. (b) Equivalent schematic with an electroneutral Na/K exchange. The outward movement of an HCO₃⁻ is equivalent to the inward movement of an H⁺ so that the movements of HCO₃⁻ and H⁺ cancel out.

this system, the following equations define the constraints.

$$x_{Na} = -x_K \tag{1}$$

$$r = -m_{Na}/m_K \tag{2}$$

$$\beta = x_{Na}/j_{Na} \tag{3}$$

$$j_{Na} + m_{Na} + x_{Na} = 0 \tag{4}$$

$$j_K + m_K + x_K = 0 \tag{5}$$

where x_{Na} and x_{K} are the electroneutral Na and K fluxes, and efflux is defined as positive. Eq. 1 constrains the exchange to be electroneutral; Eq. 2 defines the pump stoichiometry; Eq. 3 defines β as a dimensionless measure of the magnitude of the electroneutral exchange flux; and Eqs. 4 and 5 are for mass conservation of Na and K.

The passive fluxes are functions of the ionic concentrations and the membrane potential:

$$j_{\text{Na}} = P_{\text{Na}} \cdot f(E_m) \cdot (\text{Na}_o - \text{Na}_i e^\xi) \quad (6)$$

$$j_{\text{K}} = P_{\text{K}} \cdot f(E_m) \cdot (\text{K}_o - \text{K}_i e^\xi), \quad (7)$$

where $\xi = E_m F / RT$ is a dimensionless measure of the membrane potential. The function $f(E_m)$ depends on the particular model for the electric field profile across the membrane and for a constant field, $f(E_m) = \xi / (1 - e^\xi)$. However, $f(E_m)$ cancels out in the following derivation.

Using Eqs. 1-5,

$$r = \frac{-m_{\text{Na}}}{m_{\text{K}}} = \frac{-(j_{\text{Na}} + x_{\text{Na}})}{(j_{\text{K}} + x_{\text{K}})} = \frac{-(j_{\text{Na}} + \beta j_{\text{Na}})}{(j_{\text{K}} - \beta j_{\text{Na}})}.$$

Therefore,

$$\frac{j_{\text{Na}}}{j_{\text{K}}} = \frac{-r}{1 + \beta(1 - r)} = -\gamma, \quad (8)$$

where $\gamma = -j_{\text{Na}}/j_{\text{K}}$ is the ratio of the passive fluxes. Given a fixed electroneutral exchange flux² (β) and a fixed Na/K pump stoichiometry (r), Eq. 8 is the constraint placed on the ratio of the passive fluxes so that they can be balanced by the sum of the exchange and the pump fluxes. Thus, γ fulfills the same function as does r in the derivation of the MN equation in which the passive fluxes are constrained to flow in the ratio $-j_{\text{Na}}/j_{\text{K}} = r$, so that they can be balanced by the pump fluxes. Substituting Eqs. 6 and 7 into Eq. 8:

$$E_m = \frac{RT}{F} \ln \left[\frac{\gamma \cdot P_{\text{K}} \cdot \text{K}_o + P_{\text{Na}} \cdot \text{Na}_o}{\gamma \cdot P_{\text{K}} \cdot \text{K}_i + P_{\text{Na}} \cdot \text{Na}_i} \right], \quad (9)$$

which, as expected, has the same form as the MN equation but with r replaced by γ . If $\beta = 0$ (no electroneutral exchange), then $\gamma = r$, and Eq. 9 reduces to the MN equation. Similarly, if $r = 1$ (electroneutral Na/K pump), then $\gamma = 1$, and Eq. 9 reduces to the MN equation with $r = 1$, regardless of the value of β . Therefore, electroneutral Na/K exchange only affects E_m in the presence of an electrogenic Na/K pump. This reflects the fact that the greater the passive Na influx, the greater the pump rate required to maintain a constant Na_i , and, therefore, the greater the electrogenic component of E_m . In other words, changes

² Strictly speaking, since $\beta = x_{\text{Na}}/j_{\text{Na}}$ and j_{Na} is a function of E_m , β will vary with E_m even when x_{Na} is fixed. The assumption of β being set independently of E_m does not invalidate the argument; the problem is treated more fully below.

in membrane potential are generated by the Na/K pump response as the system endeavors to maintain a concentration steady state.

Although Eq. 9 appears to be formally equivalent to the MN equation, it is actually quite different. As can be seen from Eqs. 3 and 6, β (and hence γ) is a function of E_m even for a constant x_{Na} , whereas in the MN equation, r is fixed. Moreover, Eq. 9 is transcendental in E_m as can be shown by substituting Eq. 6 in its constant field form into Eq. 9. Another difference is that r in the MN equation must be positive, whereas $\gamma (= -j_{Na}/j_K)$ in Eq. 9 can be negative (Fig. 2). At first sight, the singularity occurring in Fig. 2 at $\beta = 2$ may appear unphysiological, but this represents the point at which $x_K = m_K$ ($j_K = 0$) and this occurs when $E_m = E_K$.

The existence of a region of negative γ is an interesting consequence of a large electroneutral flux. As x_{Na} increases, the bulk of the increase must be offset by m_{Na} because variations in E_m affect j_{Na} less than j_K : this can be deduced from Eqs. 6 and 7 since $P_{Na} \ll P_K$ and $Na_o/Na_i \gg K_o/K_i$. Linked to these increases in

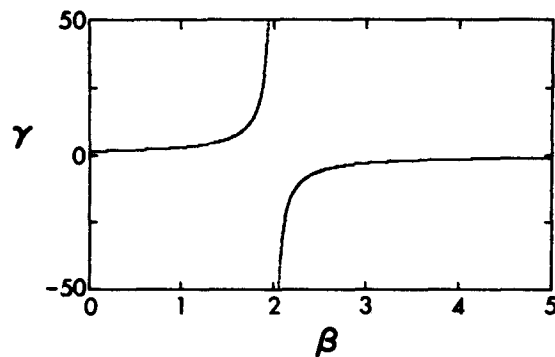


FIGURE 2. Relation between $\beta = x_{Na}/j_{Na}$ and $\gamma = j_{Na}/j_K$ calculated for $r = 3/2$. Both variables are dimensionless.

x_{Na} and m_{Na} are increases in x_K (equal to the increase in x_{Na}) and m_K . Because $r > 1$, m_K increases less than m_{Na} (and hence less than x_{Na}) and the discrepancy between m_K and x_K has to be balanced by j_K . Inevitably, a point is reached when x_K becomes so large that the only way Eq. 5 can be satisfied is for j_K to become negative (i.e., *inward* passive K flux). This, implies that E_m must become negative to E_K . The theoretical limit to this type of behavior is when $E_m \rightarrow -\infty$ as the membrane tries to compensate the increasing electroneutral exchange flux with an increasing inward potassium flux. In practice, the Na/K pump rate will saturate and this will limit the degree to which the pump can drive E_m below E_K .

The incorporation of an electroneutral exchange into the system has altered the balance between the ratio of the active fluxes ($r = -m_{Na}/m_K$) and the ratio of the passive fluxes ($\gamma = -j_{Na}/j_K$). In the MN equation, γ must equal r for the maintenance of a concentration steady state; otherwise the Na/K pump, no matter what its rate, will be unable to balance j_{Na} and j_K simultaneously. On the other hand, in Eq. 9, to enable the system to maintain a concentration steady

state, γ must now differ from r in a manner determined by the magnitude of the electroneutral exchange.

Eq. 9 is useful conceptually but is inconvenient for calculation because of its transcendental nature. An alternative form can be derived from Eqs. 1-7 in conjunction with the constant field expression for $f(E_m)$:

$$E_m = \frac{RT}{F} \ln \left[\frac{rP_K \cdot K_o + P_{Na} \cdot Na_o - \frac{x_{Na} \cdot (r-1)}{\xi}}{rP_K \cdot K_i + P_{Na} \cdot Na_i - \frac{x_{Na} \cdot (r-1)}{\xi}} \right] \quad (10)$$

Eq. 10 is still transcendental in E_m , but for calculation purposes it can be inverted to give an analytical function for x_{Na} as a function of the other variables. This has been used to calculate the family of curves in Fig. 3, which show how E_m

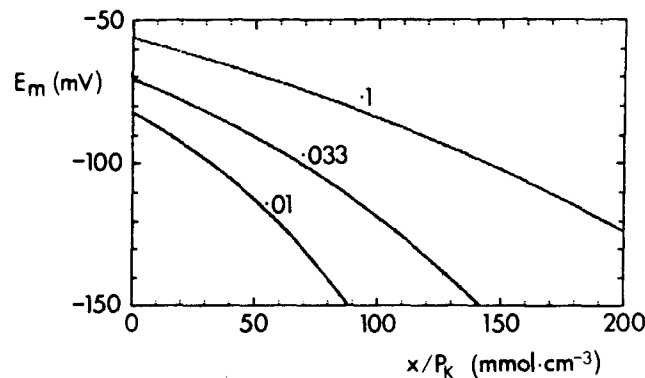


FIGURE 3. Dependence of E_m on x_K where x_K is expressed relative to P_K . Calculated for (mM) $Na_i = 12$, $K_i = 130$, $Na_o = 144$, and $K_o = 5.4$. The numbers adjacent to the curves are the values of P_{Na}/P_K .

depends on the electroneutral exchange flux for various values of P_{Na}/P_K : small values of P_{Na}/P_K make E_m more sensitive to the exchange flux magnitude.

El-Sharkaway and Daniel (1975) considered the contribution of an electrogenic pump (with no electroneutral exchanges) to the membrane potential in the non-steady state and obtained (neglecting their P_{Cl} terms):

$$E_m = \frac{RT}{F} \ln \left[\frac{P_K \cdot K_o + \left(1 - \alpha + \frac{\alpha}{r}\right) \cdot P_{Na} \cdot Na_o}{P_K \cdot K_i + \left(1 - \alpha + \frac{\alpha}{r}\right) \cdot P_{Na} \cdot Na_i} \right], \quad (11)$$

where $\alpha = -m_{Na}/j_{Na}$. Eq. 11 is the same as Eq. 9 except that β is replaced by $\alpha - 1$, leading to $1/\gamma = 1 - \alpha + \alpha/r$. The reason for this similarity is that both equations result from the relaxation of the constraint, $j_{Na}/j_K = m_{Na}/m_K$ (i.e., $\gamma =$

r), in one case because of the introduction of an electroneutral exchange (Eq. 9), and in the other by allowing a non-steady state (Eq. 11).

Na/H Exchange

In most cell systems, metabolically produced protons have to be extruded, and in many cases the Na/H exchanger has been identified as the mechanism by which this is done.

In cell systems that have a low free Cl^- permeability (e.g., cardiac muscle [Piwnica-Worms et al., 1983], nerve [Junge, 1981]) the Cl/HCO_3 exchange and the (K + Cl) cotransport would have to run at almost the same rate to maintain the steady state Cl concentration, whereas the Na/H exchange is free to run at a different rate. Indeed, if the Na/H exchange runs at the same rate as the other exchangers, then no acid equivalents will be pumped out of the cell.

Consider, for the sake of discussion, a cell with low proton permeability and the Na/H exchange as the only electroneutral exchanger. Defining the Na/H exchange flux as $x_{\text{Na}} = \epsilon \cdot j_{\text{Na}}$ and combining this with Eqs. 2, 4, and 5 (but omitting the x_{K} term in Eq. 5) gives $\gamma = r/(1 + \epsilon)$, which implies that $\gamma < r$ and hence that the membrane potential is less negative than predicted by the MN equation. As with the previous case of an electroneutral Na/K flux, the presence of an electroneutral Na flux has upset the balance between the passive electrodiffusive fluxes for Na and K: in this case, however, the effect is a depolarization. This is contrary to what may be predicted intuitively by linking an increased Na influx to stimulation of the electrogenic Na/K pump: although in the short term (i.e., non-steady state) an increased Na/H exchange may stimulate the Na/K pump to hyperpolarize the membrane, in the long term the ratio of passive Na and K fluxes (γ), and not the pump rate, will determine E_m .

Returning to a membrane that possesses all three exchangers and for which the Na/H exchanger is running faster than the other two, the Na/H exchange can be divided into a part that matches the Cl exchange flux (x'_{Na}) and a part that is in excess (x''_{Na}). The matching part ($x'_{\text{Na}} = \beta \cdot j_{\text{Na}}$) sums with the other electroneutral fluxes to give a net electroneutral Na/K exchange while the remainder ($x''_{\text{Na}} = \epsilon \cdot j_{\text{Na}}$) pumps protons out of the cell. We have discussed these two cases in isolation and it is a trivial matter to show that, when combined, γ is given by:

$$\gamma = r/[1 + \beta(1 - r) + \epsilon].$$

This shows that, depending on the relative magnitudes of β and ϵ (i.e., x'_{Na} and x''_{Na}), the membrane potential may be more or less negative than that predicted by the MN equation.

Electroneutral Na/Ca Exchange

Other electroneutral exchangers may also affect membrane potential. Consider, for the sake of discussion, the different effects on E_m of maintaining low Ca_i either by an electroneutral Na/Ca exchange or by an electrogenic Ca-ATPase pump (Fig. 4). In the case of a Ca-ATPase, the Ca pump flux, m_{Ca} , is regulated to exactly balance the diffusive flux, j_{Ca} , and Eq. 9 still applies, so that neither term will directly affect the membrane potential. In the case of a Na/Ca exchange,

we have

$$m_{\text{Na}} + j_{\text{Na}} + x_{\text{Na}} = 0 \quad (4)$$

$$m_{\text{K}} + j_{\text{K}} = 0 \quad (12)$$

$$j_{\text{Ca}} + x_{\text{Ca}} = 0 \quad (13)$$

$$x_{\text{Na}} = -2x_{\text{Ca}} \quad (14)$$

and the constant field expression for j_{Ca} (Sjodin, 1980):

$$j_{\text{Ca}} = \frac{P_{\text{Ca}} \cdot 2\xi}{1 - e^{2\xi}} (\text{Ca}_o - \text{Ca}_i e^{2\xi}). \quad (15)$$

From Eqs. 2, 4, and 12-14,

$$r = \frac{-m_{\text{Na}}}{m_{\text{K}}} = \frac{-(j_{\text{Na}} + x_{\text{Na}})}{j_{\text{K}}} = \frac{-(j_{\text{Na}} + 2j_{\text{Ca}})}{j_{\text{K}}}$$

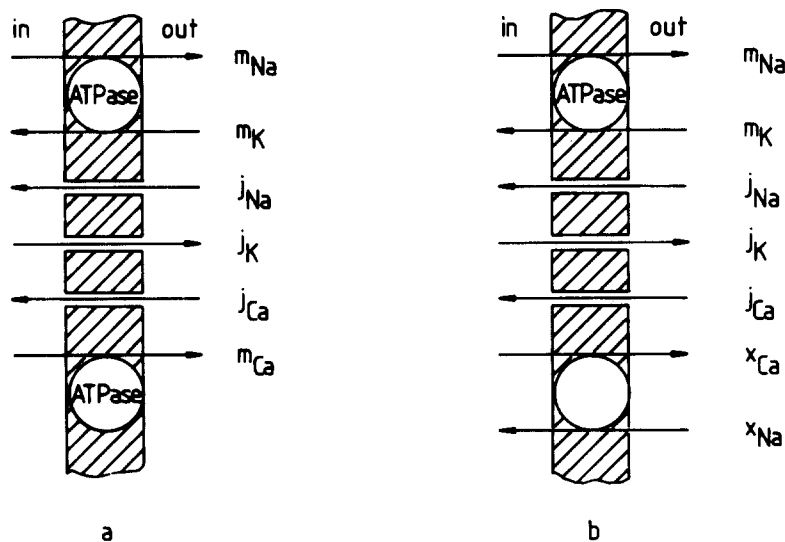


FIGURE 4. (a) Schematic for the maintenance of low Ca_i by a Ca-ATPase. (b) Schematic for the maintenance of low Ca_i by Na/Ca exchange.

or $rj_{\text{K}} + j_{\text{Na}} + 2j_{\text{Ca}} = 0$. Using Eqs. 6, 7, and 15, this gives an extension of the MN equation that includes P_{Ca} :

$$E_m = \frac{RT}{F} \ln \left[\frac{4P'_{\text{Ca}} \cdot \text{Ca}_o + rP_{\text{K}} \cdot \text{K}_o + P_{\text{Na}} \cdot \text{Na}_o}{4P''_{\text{Ca}} \cdot \text{Ca}_i + rP_{\text{K}} \cdot \text{K}_i + P_{\text{Na}} \cdot \text{Na}_i} \right], \quad (16)$$

where $P'_{\text{Ca}} = P_{\text{Ca}}/(1 + e^{\xi})$ and $P''_{\text{Ca}} = P_{\text{Ca}}/(1 + e^{-\xi})$.

Eq. 16 has been derived by Sjodin (1980), and when compared with Eq. 9, it suggests that a membrane with an electroneutral Na/Ca exchange may have a different membrane potential from that of a membrane with a Ca-ATPase: the Na/Ca exchange will shift E_m toward E_{Ca} (i.e., will depolarize the membrane) by an amount dependent on P_{Ca} .

Sjodin interprets Eq. 16 as showing that an electroneutral Na/Ca exchange does not affect membrane potential. However, his statement relates to a comparison between the case where an electrodiffusive Ca flux is balanced by an electroneutral Na/Ca exchange and the case where the electrodiffusive Ca flux is not balanced by any exchange or pump.

DISCUSSION

We have considered simple systems with fixed Na/K pump stoichiometry and negligible free chloride ion permeability. When these systems are in a concentration steady state, an electroneutral exchange can affect the membrane potential provided the exchange involves either Na or K. A net electroneutral exchange of Na for K operating in parallel with an electrogenic Na/K pump will hyperpolarize the membrane and could lead to a steady state in which E_m is negative to E_K . The hyperpolarization is generated by the electrogenic pump current as the pump rate increases to maintain the concentration steady state. On the other hand, a net electroneutral exchange involving either Na or K against a third cation (e.g., Na/Ca exchange) will shift E_m toward the Nernst potential for the third cation. Any ionic exchange can also indirectly affect membrane potential by altering the ionic distributions. In contrast, for a system in which the only constraint is that the net current is zero (i.e., flux steady state), the exchange cannot enter into the membrane potential equation because an electroneutral exchange cannot contribute to the net current.

Thus, when cells are constrained to operate in a concentration steady state, the membrane potential may be affected by electroneutral exchanges so that E_m can either be positive or negative to the value predicted by the MN equation. When searching for such an effect, it is tempting to consider changes in metabolic rate that may well entail a change in the rate of proton production. However, interpretation of such experiments is complicated by changes in E_m caused by changes in the internal ionic concentrations, as well as effects of electrogenic cotransport mechanisms [e.g., (Na + glucose) and (Na + amino acid) cotransports (Gunn, 1980)].

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