Contribution of Na/Ca Transport to the Resting Membrane Potential

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ABSTRACT   Relations are derived that describe the combined effects of electrodiffusion, the Na/K pump, and Na/Ca transport by carrier on the resting membrane potential. Equations are derived that apply to both steady-state and non-steady-state conditions. Some example calculations from the equations are plotted at different permeability coefficient ratios, $P_K : P_{Ca} : P_{Na}$. The equations predict a depolarizing action of Na/Ca transport when more than two Na ions per Ca ion are transported by the carrier. For all permeability ratios examined, a steady state for Ca ions is achieved with at most a few millivolts of depolarization.

The well-known relation for the membrane potential in terms of ionic permeabilities is not precise if ionic pumps and transport mechanisms contribute significantly to the potential (Goldman, 1943; Hodgkin and Katz, 1949). The original equation has since been modified to include the contribution of an electrogenic Na/K pump to the membrane potential (Mullins and Noda, 1963; Sjodin and Ortiz, 1975). A widely found mechanism in cell membranes transports Na ions inwardly and Ca ions outwardly in an electrogenic fashion (Blaustein et al., 1974; Mullins and Brinley, 1975; Mullins, 1977). The present purpose is to determine relations for the membrane potential that include the previously mentioned mechanisms and electrogenic Na/Ca transport as well. Some relations for the membrane potential in which permeability to Ca ions has been taken into account have been developed by Meves and Vogel (1973) and Reuter and Sholz (1977).

Inasmuch as Ca ions play a key role in an increasing number of membrane processes, it is first useful to determine the contribution of Ca ion permeability to the membrane potential on a purely passive electrodiffusional basis. This is done in the usual way by determining the condition for charge balance of the passive fluxes. For a constant electrical field across the membrane, the general equation for ionic flux is

$$ j_n = P_n \left(\frac{zVF}{RT} \right) \left[\frac{[C_n]_o - [C_n]_i e^{zVF/RT}}{1 - e^{zVF/RT}} \right], \tag{1} $$

where n refers to any ion to which the membrane is permeable, j to flux, P to permeability coefficient, z to ionic valence and V to membrane potential. All other symbols have their usual meaning. The first equation sought is obtained

by solving the sum $2j_{Ca} + j_K + j_{Na} + j_{Cl} = 0$, substituting values from Eq. 1. The expression for V, with Ca permeability taken into account, is, ignoring surface potentials near the membrane,

$$V = \frac{RT}{F} \ln \frac{4P'_{Ca}[Ca]_o + P_K[K]_o + P_{Na}[Na]_o + P_{Cl}[Cl]_i}{4P''_{Ca}[Ca]_i + P_K[K]_i + P_{Na}[Na]_i + P_{Cl}[Cl]_o}, \quad (2)$$

where

$$P'_{Ca} = P_{Ca}(e^{VF/RT} + 1)^{-1} \quad (3)$$

and

$$P''_{Ca} = P'_{Ca}e^{VF/RT} \quad (4)$$

A similar equation appears in the literature (Reuter and Scholz, 1977; Lewis, 1979), but the reader should note an error in the first reference. As presented by these authors, the equation fails to reduce to the calcium equilibrium potential for a perfectly Ca-selective membrane. Given the form of Eq. 1 for divalent cations, it is unfortunately not possible to obtain a solution having the form of Eq. 2 without defining potential-dependent "apparent" permeability coefficients P'_{Ca} and P''_{Ca}. The transcendental nature of Eq. 2 means that solutions have to be made by simple trial and error or by computer using Eqs. 3 and 4. For normal values of the resting potential (−70 mV to −90 mV), however, $P'_{Ca} \cong P_{Ca}$. It can easily be verified that Eq. 2 reduces to the equilibrium potential for Ca ions for a perfectly Ca-selective membrane:

$$V_{Ca} = \frac{RT}{2F} \ln \frac{[Ca]_o}{[Ca]_i}. \quad (5)$$

An "extended constant-field equation" that does not employ potential-dependent "permeability" coefficients and that does include permeability to divalent ions also appears in the literature (Piek, 1975; Jan and Jan, 1976).

To take into account the other membrane mechanisms, the following symbols are used: m_{Na}, Na pump flux; m_K, K pump flux; t_{Na}, Na flux by Na/Ca transport; and t_{Ca}, Ca flux by Na/Ca transport. The convention of positivity for efflux is used. The normal direction for Na/Ca transport is outward for Ca and inward for Na. Thus, t_{Ca} is normally positive and t_{Na} negative.

Steady-State Solution

This relation is obtained by assuming that electrodiffusional leaks for Na, K, and Ca, a Na/K pump, and Na/Ca transport fluxes produce a state of flux balance such that values of $[Na]_i$, $[K]_i$ and $[Ca]_i$ do not change. Under normal conditions, this can be visualized as a state in which Ca ions leaking in are balanced by outward Ca transport, Na ions leaking in and transported inwardly by Na/Ca transport are balanced by an outward Na pump, and K ions leaking out are balanced by an inward K pump. All equations will be derived for these cations only for the purpose of abbreviating derivations. It will be obvious how the addition of the chloride leak j_{Cl} will modify the results.

Active Cl transport is not considered. For ionic concentrations not to change, the following relations must hold:

$$j_{Ca} = -t_{Ca},$$ (6)

$$j_{Na} + t_{Na} = -m_{Na}, \quad \text{and}$$ (7)

$$j_K = -m_K.$$ (8)

The Na/K pump coupling ratio, r, has been defined (Mullins and Noda, 1963):

$$r = -\frac{m_{Na}}{m_K}.$$ (9)

The stoichiometric factor, q, for Na/Ca transport is the number of Na ions transported per Ca ion:

$$q = -\frac{t_{Na}}{t_{Ca}}.$$ (10)

To obtain the required steady-state solution, the sum $j_{Na} + j_K + 2j_{Ca} + m_K + m_{Na} + 2t_{Ca} + t_{Na}$ is set $= 0$ to fulfill electrical neutrality. Substitutions are made from Eq. 1 and from Eqs. 6–10. The resulting equation for V is:

$$V = \frac{RT}{F} \ln \frac{2qP'_{Ca}[Ca]_o + rP_K[K]_o + P_{Na}[Na]_o}{2qP''_{Ca}[Ca]_i + rP_K[K]_i + P_{Na}[Na]_i}$$ (11)

It is of interest to note some features of Eq. 11. If the stoichiometric ratio q = 2, two Na ions are transported per Ca ion and Na/Ca transport is electrically neutral. In this case, Eq. 11 reduces to Eq. 2, where Ca ions exert only their passive electrodiffusional effect. The actual value for q appears to be 4 (Mullins, 1977). In this case, the terms due to Ca are twice those due to the electrodiffusional effect of Ca ions. For the values of $[Ca]_i$ in resting excitable cells, the effect of Na/Ca transport is an additional depolarization numerically equivalent to that obtained by doubling the value of either P_{Ca} or $[Ca]_o$ in the absence, of course, of changes in P_K. The source of the depolarization is the inward transport of two charges during each cycle of Na/Ca transport operation. The precise equivalency in the case of the electrical effects of j_{Ca} and Na/Ca transport is, of course, due to the fact that t_{Ca} just balances j_{Ca} and that the net charge on the Na/Ca carrier happens to equal 2, the valence of Ca ions. Similar interpretations can be made for other values of q. It should also be noted that, given the very low values for $[Ca]_i$ in most excitable cells, the calcium term on the bottom of Eq. 11 can probably safely be ignored.

Non-Steady-State Solution

When ionic concentrations are permitted to change, Eqs. 6–8 must be modified. The ratio of transport rate to leakage rate, f, can be defined for Ca ions by the relation:

$$f_{Ca}j_{Ca} = -t_{Ca}.$$ (12)

Similarly, for K ions:

$$f_K j_K = -m_K. \tag{13}$$

For Na ions, the factor f_{Na} must also include the inward movement due to Na/Ca transport:

$$f_{Na}(t_{Na} + j_{Na}) = -m_{Na}. \tag{14}$$

Applying the same condition for electrical neutrality applied previously and substituting from Eqs. 9, 10, and 12-14 yields:

$$q f_{Ca} j_{Ca} + \frac{f_K}{f_{Na}} r j_K + j_{Na} = 0. \tag{15}$$

Eq. 15 is the algebraic summary statement of the condition for electrical neutrality. This equation clearly places restrictions upon the values that f_{Ca}, f_K and f_{Na} can assume. If, for example, one is in the steady state, and the Ca transport rate is increased such that f_{Ca} assumes a value different from unity, the remaining fluxes must become adjusted in such a way that Eq. 15 is obeyed. Making substitutions for j values from Eq. 1 and solving for V,

$$V = \frac{RT}{F} \ln \frac{2 q f_{Ca} P'_{Ca}[Ca]_o + r\frac{f_K}{f_{Na}} P_K[K]_o + P_{Na}[Na]_o}{2 q f_{Ca} P''_{Ca}[Ca]_i + r\frac{f_K}{f_{Na}} P_K[K]_i + P_{Na}[Na]_i}, \tag{16}$$

which gives the membrane potential for non-steady-state conditions. If one knows the coupling ratios for the two transport processes and the magnitudes of all the flux components, one can compute the value of the membrane potential, provided ionic permeability coefficients and concentrations are known. The equation for the steady state, 11, can be regarded as a special case of Eq. 16, for which $f_{Ca} = f_K = f_{Na} = 1$.

It is of interest to consider some properties of Eq. 16. Increasing the value of f_{Ca} above 1.0, meaning that more Ca ions are transported outwardly than leak inwardly, results from Eq. 16 in increasing depolarization from the Ca term. The reason is that the increased Ca transport must be accompanied by an increased inward movement of charge via the Na/Ca carrier.

The change in membrane potential resulting from a change in the Ca transport rate via the Na/Ca carrier depends upon the nature of the flux readjustments. The presence of three mechanisms for ion movement makes it possible for electrical neutrality to be achieved in a variety of ways. To obtain useful solutions to Eq. 16, careful attention must be paid to the physiological events occurring during a readjustment of the ionic fluxes. To illustrate the use of Eq. 16, the membrane potential can be plotted as a function of increasing Na/Ca transport rate for different permeability coefficient ratios. This is done in Fig. 1, where permeability coefficients and ionic concentrations remain constant for each curve. The potential plotted is, therefore, the instantaneous value assumed when the indicated Ca transport rate occurs before ionic concentrations have had a chance to change. The value of the
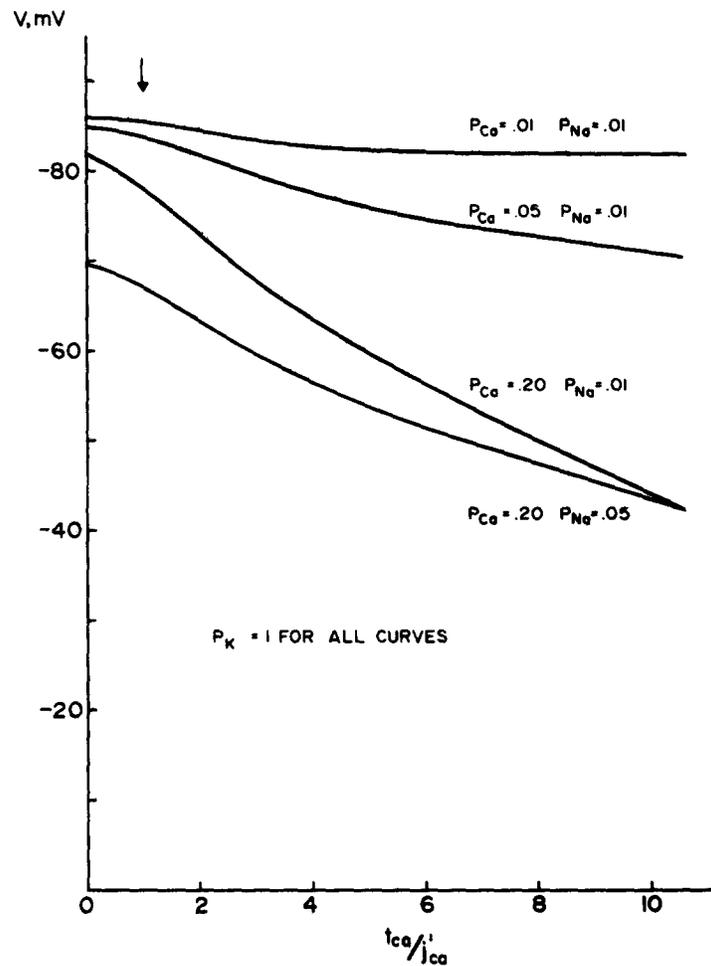
FIGURE 1.   Calculated values of the membrane potential are plotted against increasing calcium transport rate, i_{Ca}, expressed as the fraction i_{Ca}/j'_{Ca}, where j'_{Ca} is the passive inward calcium ion leak in the steady state (marked by the arrow). At $i_{Ca} = 0$, Eq. 2 was used with P_K replaced by rP_K and P_{Cl} terms ignored. In the steady state, Eq. 11 was used. All remaining values were calculated from Eq. 16, with the aid of Eq. 15. Ion electrodiffusion rates were calculated using Eq. 1 with the following ionic concentrations in millimolar units: $[Na]_o = 150$, $[K]_o = 5$, $[Ca]_o = 2$, $[Na]_i = 10$, $[K]_i = 150$. The normal value of $[Ca]_i$ is about $0.1~\mu M$ or less, making the Ca term in the denominator negligible in all cases. The value of P_K was normalized to 1.00 for all calculations. Curves are plotted for various representative permeability coefficient ratios. The value used for the Na/Ca transport stoichiometric ratio, q, was 4.0 for all calculations. The Na/K pump stoichiometric ratio, r, was taken to be 1.5 for all calculations. Temp. = $37°C$.

potential for zero Na/Ca transport rate is simply the appropriate solution of Eq. 2. The system is not in a steady state at this point. At the point t_{Ca}/j_{Ca} = 1, the system was chosen to be in the steady state for Na, Ca, and K ions. The potential is the solution of Eq. 11. It should be noticed that the steady state for Ca ions for all permeability ratios plotted is achieved at the cost of only a few millivolts of depolarization. Because ionic concentrations are not permitted to change for these curves, the Na/K pumping rate remains constant, and the increased inward charge movement due to the Na/Ca carrier must be balanced by ionic electrodiffusional leaks. If we consider the passage of time, however, the value of $[Na]_i$ must increase as a net Na influx must occur when $t_{Ca}/j_{Ca} > 1$ under the assumed conditions. As $[Na]_i$ rises, the Na/K pump rate rises if the pump has not reached the saturation rate. Under these conditions, the hyperpolarizing effect of the Na pump becomes apparent by causing some of the increased Na/Ca transport charge to be balanced by Na outward pumping rather than by ionic leaks. These changes of potential are illustrated in Fig. 2 for $P_K : P_{Ca} : P_{Na}$ = 1:0.2:0.01. At the point marked by the arrow, the steady state is perturbed by increasing the t_{Ca}/j_{Ca} ratio from 1 to 10. As $[Na]_i$ rises, the increased level of Na/K pump operation produces hyperpolarization. The value of $[Na]_i$ can only rise, however, until the Na pump balances the Na leakage in, plus the new value of the Na influx by Na/Ca transport. At this point Na ions are in a new steady state and further hyperpolarization cannot occur. Not all of the increased inward charge movement by Na/Ca transport has been compensated by the pump at this point, however. The remainder must be compensated by electrodiffusive fluxes, mainly those due to K^+. The final potential reached is thus a steady state for Na but not for K and Ca whose net fluxes balance at the final potential reached.

Another feature of Eq. 16 is that the value of f_{Ca} need not be positive. Inasmuch as the value of j_{Ca} is always in the inward direction for values of V more negative than V_{Ca}, f_{Ca} becomes negative if the direction of Na/Ca transport is reversed when V is in this range (Eq. 12). It is known that Na/Ca transport can operate in the reversed mode under certain conditions (Baker et al., 1969). Under these conditions, Na ions are transported outwardly over the Na/Ca carrier, and Ca ions are transported inwardly. According to Eq. 16, the reversed direction of Na/Ca transport gives rise to a hyperpolarizing effect as f_{Ca} is now negative, and the Ca term in the numerator subtracts numerically from the other terms. The source of the hyperpolarization is the now outward movement of charge by the Na/Ca carrier. Readjustments of the Na/K pump have to be taken into account here as well. Also, it should be noted that permeability to chloride ions can be taken into account by adding $P_{Cl}[Cl]_i$ to the numerators and $P_{Cl}[Cl]_o$ to the denominators of the logarithmic terms in Eqs. 11 and 16.

DISCUSSION

Eqs. 11 and 16 should find application whenever the membrane has an appreciable permeability to Ca ions and Na/Ca transport forms a significant fraction of the total traffic of ionic flux across the membrane. The most likely
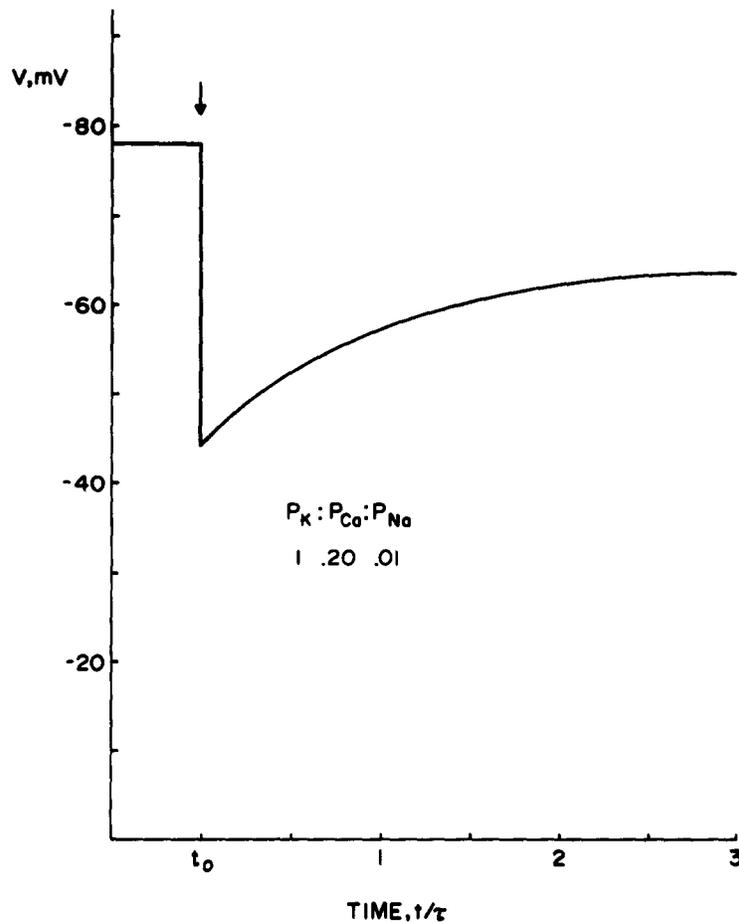
FIGURE 2.   The calculated resting membrane potential is plotted vs. time when the steady state (arrow) is perturbed by a sudden 10-fold increase in the Ca outward transport rate. The stoichiometry of Na/Ca transport demands an accompanying 10-fold increase in the Na inward transport rate by the Na/Ca carrier. The time is plotted as the ratio t/τ, where τ is the time constant for the increase in $[Na]_i$ that results from the increased inward Na movement due to increased Na/Ca transport rate. It is assumed that the Na pump operates in the linear region, giving an increment in pumped efflux that is proportional to the increment in $[Na]_i$. Under these conditions, the kinetics are exponential, and the time constant is $\tau = \left(\dfrac{V}{A}\right) \dfrac{[Na]_i'}{J_{Na}}$, where V/A is the volume to surface ratio of the fiber, $[Na]_i'$ is the final value of $[Na]_i$ reached at Na flux balance and $J_{Na} = j_{Na} + t_{Na}$, the total new Na influx value. It is assumed that any volume changes can be neglected. A 4% decline in the Na electrochemical gradient due to elevation of $[Na]_i$ has also been neglected, and the Na/Ca transport rate has been assumed to remain constant. If these assumptions are changed, more complicated kinetics can result. If the Na pump saturates before the $[Na]_i$ value required for Na flux balance is reached, the membrane potential in Fig. 2 will level off at a more depolarized value of potential, where more of the increased inward charge movement due to Na/Ca exchange will have to be balanced by K^+ outward leak. The text should be consulted for further details.

candidates for cells that might provide these conditions are those excitable cells in which Ca ions play a role in action potential generation such as cardiac Purkinje fibers (Reuter, 1967; Aronson and Cranefield, 1973; Kass et al., 1976) and invertebrate muscle fibers (Fatt and Ginsborg, 1958; Hagiwara et al., 1964). In Purkinje fibers, the resting potential has been found to remain well below V_K and to be relatively insensitive to changes in $[K]_o$, even in an Na-free medium (Aronson and Cranefield, 1973). One effect of exposure to Na-free media would be a reduction in $[Na]_i$ that could result in a reduction or complete loss of the electrogenic Na-pump contribution to the resting potential. Indeed, Wiggins and Cranefield (1974) have reported that readmission of Na to the medium under these conditions results in hyperpolarization of the membrane. The relative insensitivity of the resting potential to $[K]_o$ in Na-free solutions might also be a reflection of a significant permeability to Ca ions at rest. A variability in the results noted in Na_o-free experiments has also been noted (Cranefield, 1975). Varying contributions of Na/Ca exchange and Na pumping to the resting potential under these conditions might play a role in these examples. The present equations for the resting potential may be applicable in these cases, and experiments of this sort should perhaps be reinterpreted and amplified to test the possible role of Na/Ca exchange in the analysis of results.

The significant contribution of electrogenic Na extrusion to the resting potential of cardiac Purkinje fibers is very clearly indicated in the work of Gadsby and Cranefield (1979 b), where the addition of 4 mM $[K]_o$ to fibers in a previously K-free medium results in a transient hyperpolarization. Any contribution of Na/Ca exchange to the resting potential in this preparation could be studied by varying [Na] and [Ca] in suitable experiments in the presence of 10^{-5} M strophanthidin, which abolishes the outward current transient due to Na-pump electrogenicity in Purkinje fibers (Gadsby and Cranefield, 1979 a; Eisner and Lederer, 1980). The present equations may prove helpful in sorting out Na/Ca counter transport contributions to the resting potential of Purkinje fibers from contributions due to the electrogenic Na pump and the K-electrode properties of these membranes.

In barnacle muscle fibers, which give Ca-action potentials under appropriate conditions, removal of Na_o has been reported to give rise to some 10 mV of hyperpolarization (Hagiwara et al., 1964). The result has been taken to indicate a significant permeability to Na ions. In the absence of measurements of P_{Na}, such a conclusion now seems questionable because the removal of Na/Ca exchange can also cause hyperpolarization. Experiments on these fibers should be performed to measure the Na/Ca exchange fluxes, the value of P_{Ca}, and the relative contributions of Ca and Na to the resting membrane potential.

In the excitable fibers classically used to develop the theory of the resting membrane potential, namely, skeletal muscle fibers and invertebrate giant axons, only minimal reinterpretation of experimental results would be necessitated by the present treatment. In skeletal muscle fibers, P_{Ca} appears to be of about the same order as P_{Na} (Bianchi and Shanes, 1959). The upper curve in Fig. 1 should approximate this case, showing relative independence of the

resting potential from Na/Ca exchanges. The depolarization required to balance the Ca fluxes by Na/Ca transport amounts to 0.5 mV for skeletal muscle fibers under normal conditions, thus explaining why this transport can be neglected in the theory for the normal resting potential of skeletal muscle fibers. In frog skeletal muscle (Koketsu and Noda, 1960) and lobster muscle fibers (Werman and Grundfest, 1961), the membrane potential is sensitive to the removal of external Ca ions. The results are complicated, however, by an effect of Ca ions on P_K and probably P_{Na} as well. If variations in $[Ca]_o$ influence other permeability coefficients, this must clearly be taken into account in applications of extended constant-field equations to the membrane potential of cells. In the case of normal squid giant axons, $P_{Ca} \cong 0.1 \ P_{Na}$ (Hodgkin and Keynes, 1957) so that Na/Ca transport is negligible in theoretical treatments of the resting potential for squid axons.

The present extensions of the constant-field equation take into account the major known transport processes in excitable cells. It is amply clear that the extraction of permeability coefficient ratios from membrane potential data alone is possible only after taking into account flux data for the various transport processes involved. The flux data can be obtained from electrical studies provided the proper membrane current can be positively identified. Ouabain has been useful in identifying electrogenic Na-pump currents. So far no agent has been identified that is a specific inhibitor of Na/Ca transport without effects on other Ca membrane processes. Lanthanum ions are, however, effective blockers of Na/Ca transport and may prove useful in identifying membrane currents due to this process.

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