ELECTROMOBILE SURFACE CHARGE ALTERS MEMBRANE POTENTIAL CHANGES INDUCED BY APPLIED ELECTRIC FIELDS

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ABSTRACT The relation between extracellular electric fields and changes in membrane potential that such fields directly induce has previously been described both theoretically and experimentally. It is clearly established that extracellular electric-field-induced membrane potential changes are well described by Poisson's equation of electrostatics. A modification of this simple theory to include effects of the electric-field-induced redistribution of charged cell surface components is introduced and is shown to produce major alterations in calculated membrane potential changes over times of the order of minutes to hours. Implications for biological systems which respond to extracellular electric fields are discussed.

INTRODUCTION

It has been recognized for some time that applied or endogenous extracellular electric fields interact with cells in a variety of ways. One such mode of interaction leads to a spatially dependent change in the plasma membrane potential (V_m); this effect has recently been directly demonstrated in single cells exposed to a uniform applied electric field (Gross et al., 1986; Ehrenberg et al., 1987). These studies demonstrated that the change in V_m measured in cells of simple geometry over short times ($\leq$3 s) was that predicted by Poisson's equation of electrostatics.

It has also been well established that redistribution of charged macromolecules on the cell outer surface occurs in response to an applied electric field (Jaffe, 1977; Poo, 1981). This redistribution can lead to alterations in membrane potential due to shifts of the membrane surface potential (ψ). As outlined below, the effect of the change in external surface potential can be significant, always tends to oppose the change in V_m directly induced by the field, and occurs with a characteristic time of many minutes to hours.

The Direct Effect

Fig. 1 illustrates the assumed distribution of electric potential from the inner bulk aqueous cytoplasm to the extracellular bulk aqueous phase, including the effects of the Nernstian ionic diffusion potentials (i.e., from Goldman-Hodgkin-Katz theory; Aidley, 1971) as well as surface potential (see McLaughlin, 1977). It is clear that the electric potential difference across the membrane proper (V_m) differs from the bulk-to-bulk membrane potential V by the difference in the inner and outer surface potentials, $\psi_i - \psi$. It is straightforward to show that the bulk-to-bulk potential V is simply that calculated from the Goldman-Hodgkin-Katz equation using bulk aqueous phase ion concentrations if (*a*) the Goldman-Hodgkin-Katz formalism is valid, (*b*) ions in solution near the membrane surface obey Boltzmann statistics, and (*c*) anion permeability across the membrane is much less than cation permeability (Gross et al., 1983). Thus, the potential difference falling across the membrane itself, V_m, is

$$V_m = V_{bulk} + \psi_i - \psi, \quad (1)$$

where V_{bulk} is the ion diffusion potential calculated with bulk phase ion concentration.

Application of a uniform electric field of strength E to a spherical cell of radius a will, according to Poisson's equation, directly modify V_m by the amount

$$\Delta V_m = (3/2)\, Eaf_\theta \cos\theta, \quad (2)$$

where θ is the polar angle in reference to the direction of the applied field vector,

$$f_\theta = 2\lambda_o \lambda_i / [(2\lambda_o + \lambda_m)(2\lambda_m + \lambda_i) + (a/\delta)\lambda_m(2\lambda_o + \lambda_i)],$$

λ_o, λ_i, and λ_m are the electrical conductivities of the extra- and intracellular media and the membrane, respectively, and δ is the thickness of the membrane. For most healthy cells $\lambda_o \sim \lambda_i \gg \lambda_m(\delta/a)$ so that $f_\theta = 1$ (Jaffe and Nuccitelli, 1977; Poo, 1981).

Surface Potential Redistribution

The theoretical description of electrophoresis of charged cell surface components of electrophoretic mobility m_j and diffusion coefficient D_j leads to the following expression for

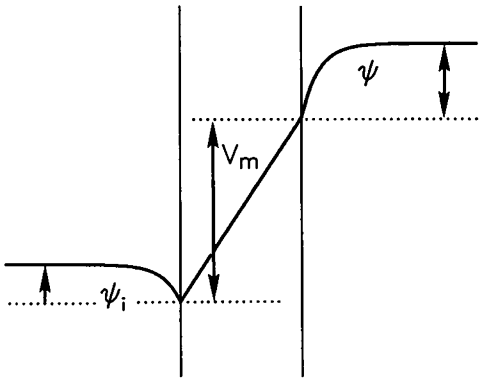

FIGURE 1 Spatial distribution of electric potential in the direction perpendicular to the plane of the membrane.

the surface concentration of mobile component j:

$$C_j = C_{o,j}[(1 - \nu_j) + \nu_j \beta_j \operatorname{csch}\beta_j e^{-\beta_j \cos\theta}], \quad (3)$$

where $C_{o,j}$ denotes the uniform surface concentration of component j with no field present, ν_j is the fraction of component j which is mobile, $\beta_j = (3/2)\,\mathrm{Ea}f_\beta(m_j/D_j)$ and $f_\beta = 2[\lambda_o\lambda_m + (\delta/a)\,\lambda_o\,(3\lambda_m + \lambda_i)]/[\lambda_m\,(2\lambda_o + \lambda_i) + (\delta/a)\,(2\lambda_o + \lambda_m)\,(2\lambda_m + \lambda_i)]$. Again the factor $f_\beta = 1$ for most cells. Based on Gouy-Chapman surface potential theory (McLaughlin, 1977), the relation between surface charge σ and surface potential is

$$\psi = (2\mathrm{RT}/\mathrm{ZF})\sinh^{-1}(\sigma/A), \quad (4)$$

where the bathing solution is assumed to be composed of ions of valence Z, R = gas constant, T = absolute temperature, $A = (8C_b\,\epsilon\mathrm{RT})^{1/2}$, C_b is the ionic concentration in the bulk aqueous phase, and ϵ is the dielectric constant of the aqueous medium (assumed constant) near the membrane surface. From Eq. 3 the net (field-dependent) surface charge can be written as

$$\sigma = \Sigma\, Z_j FC_{o,j}[\nu_j + (1 - \nu_j)\,\beta_j \operatorname{csch}\beta_j e^{-\beta_j\cos\theta}], \quad (5)$$

where Z_j is the valence of component j and F is Faraday's constant. Eqs. 4 and 5 describe the variation of surface potential due to an applied field.

In a similar manner, the variation of intracellular surface potential ψ_i with applied field can be derived. The expressions are identical with those for the extracellular surface potential with the exception that the factor f_β is replaced by

$$f_i = 2\lambda_o\lambda_m/[\lambda_m(2\lambda_o + \lambda_i) + (\delta/a)(2\lambda_o + \lambda_m)(2\lambda_m + \lambda_i)]$$

which is vanishingly small for most cells.

The Complete Model

Combining Eqs. 1, 2, 4, and 5 as well as the similar expression for intracellular surface charge leads to an expression for the change in V_m due to an applied electric field including surface charge redistribution effects. To examine the general features of this model, consider the simple case in which only one charged, monovalent cell surface component is present for a cell with $\lambda_o \sim \lambda_i \gg \lambda_m(\delta/a)$. In this case, the change in V_m in a spherical cell in response to an applied (or endogenous) uniform field is

$$\Delta V_m = (3/2)\,\mathrm{Ea}\cos\theta + \psi_o - (2\,\mathrm{RT}/\mathrm{F})\sinh^{-1}\{\sigma_o[(1 - \nu) + \nu\beta\operatorname{csch}\beta\, e^{-\beta\cos\theta}]/A\}, \quad (6)$$

where ψ_o and σ_o are the extracellular surface potential and surface charge, respectively, before application of the field. The angular dependence of the external surface potential, the last term in Eq. 6, is shown in Fig. 2 *a* for $\psi_o = -30$ mV and for several values of the mobile fraction ν. The angular dependence of ΔV_m for these same values is shown in Fig. 2 *b*. Note that at both the cathode-($\theta = 0°$) and anode-facing ($\theta = 180°$) sides of the cell, the effect of the change

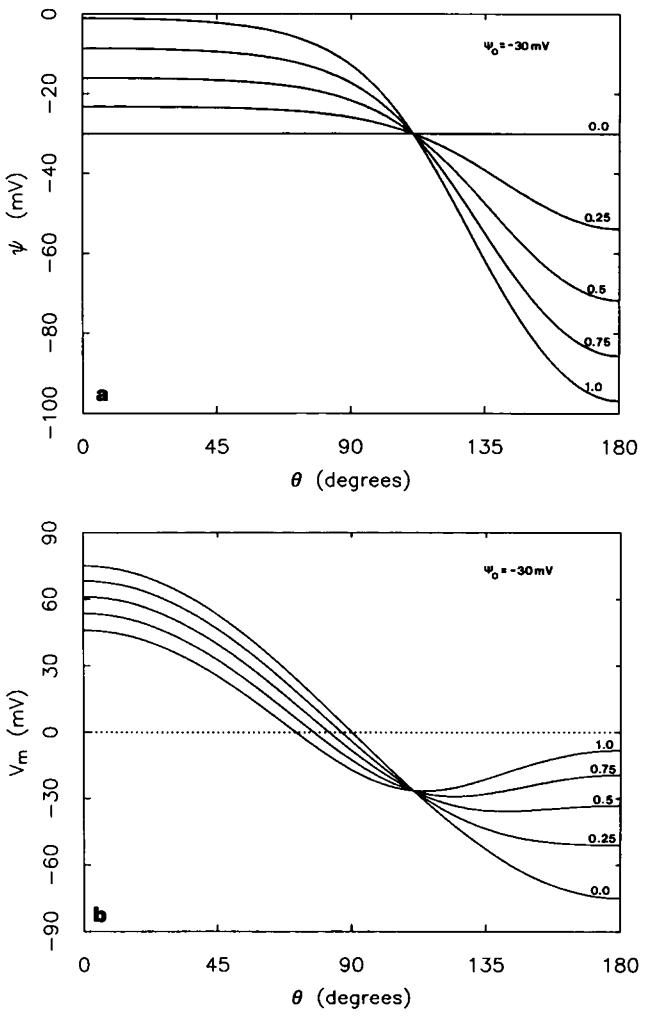

FIGURE 2 The angular dependence of external surface potential *a* and the change in transmembrane potential *b* for a 20 μm diameter spherical cell with an initial surface potential of −30 mV. The cell is exposed to a 50 V/cm uniform electric field. The predictions of Eq. 6 are shown for various fractional mobilities of surface charge as indicated. The ratio m/D is set equal to 3.3×10^{-2} mV^{-1} (Poo, 1981).

in surface potential is to oppose the change in V_m induced directly by the field.

That this compensating effect of surface potential redistribution is a general result is illustrated in Fig. 3 *a*. For various values of the mobile fraction ν are plotted the changes in membrane potential at $\theta = 180°$ for a 20 μm diameter spherical cell subjected to a 50 V/cm electric field versus the value of the zero-field surface potential. Note that the full -75 mV change in V_m due to the direct effect of the applied field is found only when surface charge is immobile or zero. The change in V_m due to the applied field is reduced for all other values of mobile fraction whether the surface potential is positive or negative. At the pole of the cell ($\theta = 90°$) where the direct effect of the applied field on ΔV_m is zero (see Eq. 2), mobile surface charge induces changes in ΔV_m (Fig. 3 *b*).

This general feature of opposition of direct changes in

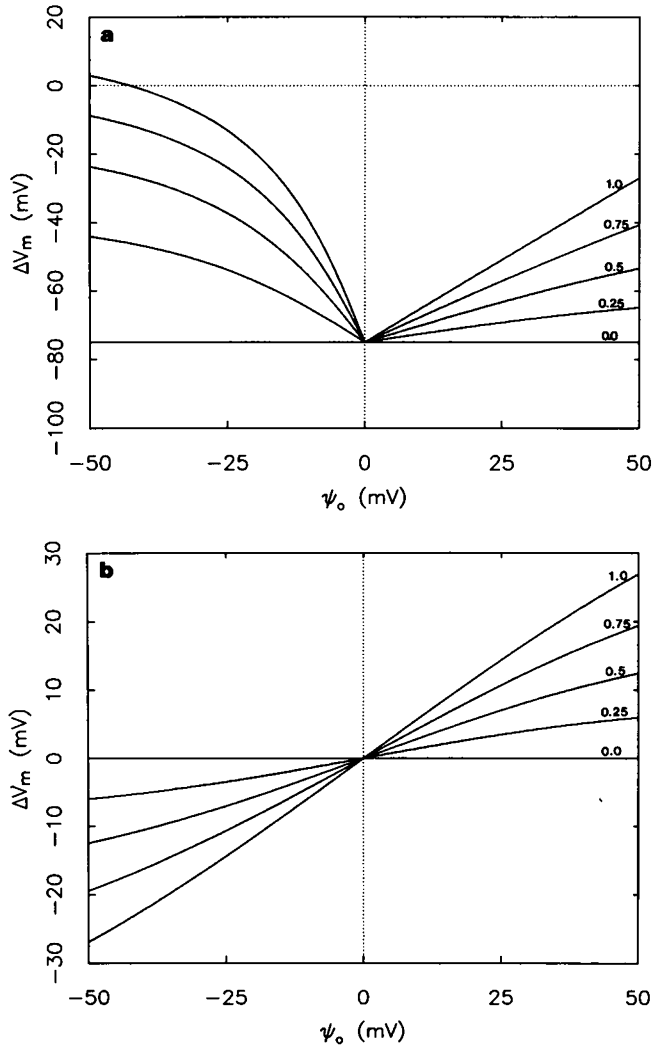

FIGURE 3 The dependence of the mobile surface charge effect on sign and magnitude of external surface potential. The change in V_m at $\theta = 180°$ *a* and $\theta = 90°$ *b* for a 20 μm diameter spherical cell exposed to a 50 V/cm uniform electric field with m/D = 3.3×10^{-2} mV^{-1}. The families of curves correspond to various fractional mobilities as indicated.

V_m by mobile surface charge redistribution is complicated in the case that internal surface charge also redistributes. For this to occur, the conductance of the plasma membrane must be great enough that the extracellular electric field penetrates into the cell interior, i.e., $\lambda_o \sim \lambda_m(\delta/a)$ and/or $\lambda_i \sim \lambda_m(\delta/a)$. In this case, the effect of extracellular surface charge redistribution is to oppose the change in V_m due to the direct action of the field while that of intracellular surface charge redistribution is to enhance the direct change in V_m. The net result, enhancement or depression of the direct change in V_m, depends on the signs and relative magnitudes of the inner and outer surface potentials, the fraction of mobile charged components on both membrane faces, and the electrical properties of the cell and its surroundings. It is interesting to note that a completely conductive plasma membrane will have no change in V_m generated due to the direct action of an extracellular field (Eq. 2) although surface charge redistribution can in principle generate a spatially-dependent change in V_m. The dependence of ΔV_m upon applied field strength is highly nonlinear and is a function of angle about the cell. Fig. 4 *a* illustrates the dependence of ΔV_m at $\theta = 0°$ upon applied field strength for $\psi = -50$ mV for a variety of values of fractional mobility. Note that the strongest nonlinearity of response occurs at lower field strengths since depletion of the surface charge at $\theta = 0°$ is nearly complete at E = 25 V/cm. These nonlinear effects are quite pronounced at various different locations on the cell (Fig. 4 *b*) as surface charge distribution is altered by the applied field.

Time Dependence

The above derivation assumes that redistribution of surface charge has reached equilibrium. However, for a step change in the applied field strength, the characteristic time of development of the direct change in V_m is quite different than that for surface charge redistribution. For the former, the characteristic time is (Ehrenberg et al., 1987)

$$\tau = aC_m(2\lambda_o + \lambda_i)/2\lambda_o\lambda_i f_\tau, \quad (7)$$

where C_m = capacitance per unit area of the membrane and $f_\tau = 1 + \lambda_m(2\lambda_o + \lambda_i)a/2\lambda_o\lambda_i\delta$ which again is 1 for most cells. The characteristic response time of the redistributing surface charge is (Poo, 1981)

$$\tau' \simeq (a^2/2D)/(1 - \beta^2/2). \quad (8)$$

For a cell of radius 10 μm with a capacitance per unit area of 1$\mu F/cm^2$ immersed in normal saline of conductivity 0.015 mho/cm, the characteristic direct electrical time constant τ is 100 ns. For mobile components on the cell surface with diffusion coefficients from 10^{-9} cm^2/s to 10^{-12} cm^2/s, τ' = 8 min to 100 h. To my knowledge, all direct or indirect measurements of E-field-induced changes in V_m to date have been over times much shorter than the above-calculated fastest surface charge redistribution time (Gross et al., 1986; Ehrenberg et al., 1987;

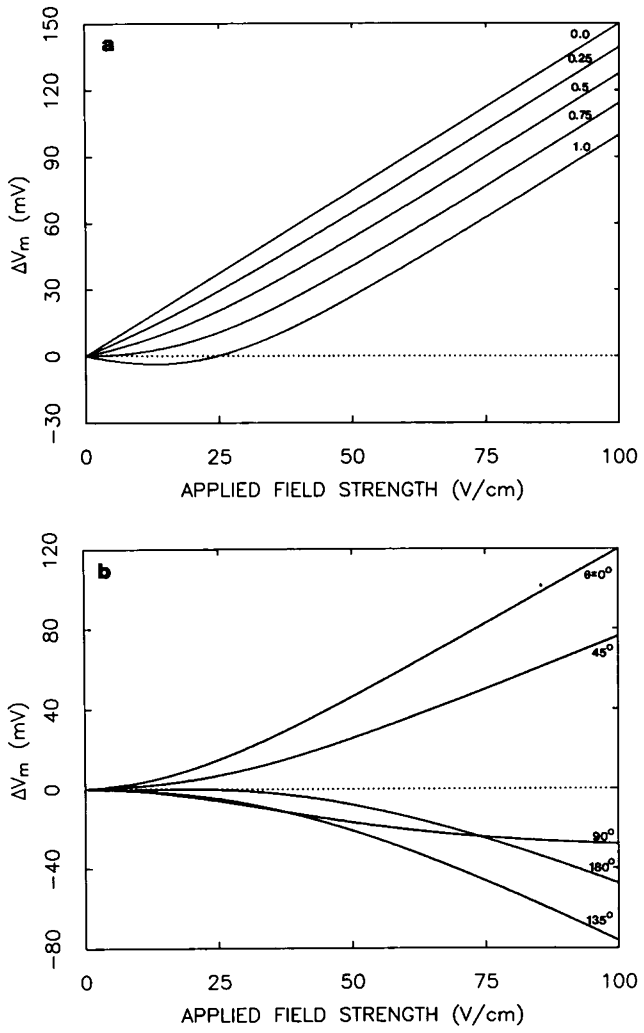

FIGURE 4 Change in V_m versus applied electric field strength in a 20 μm diameter cell for $\psi_o = -50$ mV and $\theta = 0°$ at several different fractional mobilities *a*. Panel *b* illustrates the highly nonlinear response of V_m at several positions around the cell for a completely mobile surface charge generating an initial surface potential of -30 mV. Compare with the expected linear response predicted by Eq. 2 which neglects the surface charge redistribution effect. $m/D = 3.3 \times 10^{-2}$ mV^{-1}.

Farkas et al., 1984; Benz and Zimmermann, 1980; Teissie, et al., 1982), thus it is not surprizing that the surface charge redistribution effects have not yet been found experimentally.

DISCUSSION

The theory outlined above is based on observed properties of real cells responding to external electric fields. The direct generation of changes in V_m has been well established (Gross et al., 1986; Ehrenberg et al., 1987). The appropriateness of Gouy-Chapman surface potential theory has been shown to apply to model membranes over a wide range of conditions (McLaughlin, 1977). The E-field-induced redistribution of specific cell surface constituents has been demonstrated for both glycoproteins as well as lipids (Poo, 1981; Sowers and Hackenbrock, 1981; McClosky et al., 1984). Thus, the fundamental effect of E-field-induced surface charge redistribution upon changes in V_m seems well based.

One might be concerned that electro-osmotic redistribution of surface charge discussed by McLaughlin and Poo (1981) might drastically affect one of the above conclusions, namely, that redistribution of external surface charge always opposes the direct E-field-induced change in V_m. However, according to the electro-osmotic theory, all electromobile surface components with zeta potentials more negative than the average cell surface zeta potential will move toward the anode-facing side of the cell while those more positive will move in the opposite direction. Thus, the net effect of surface charge redistribution will be the same as described above for simple electrophoresis although the magnitude of the effect might be different. Since the relationship between surface charge and zeta potential is difficult to predict for a real cell (McLaughlin and Poo, 1981), it is impossible to assess quantitatively the magnitude of this effect.

A second way in which the magnitude of the redistribution of surface charge could be different from that calculated in Eq. 3 has recently been described by Ryan et al. (1988). They showed that electrophoretic redistribution of IgE-F_c receptors on rat basophilic leukemia cells did not follow Eq. 3, but rather that these molecules showed a surface density-dependent restriction of receptor packing. Thus, the measured surface concentration of receptors moved to the high concentration side of the cell was less than predicted by Eq. 3. Such effects tend to diminish the magnitude, but not the sign, of the surface charge effect proposed here.

The underlying premise in the model described above relies on an electromobile surface charge of sufficient magnitude to modulate the direct effects of applied fields on membrane potential. It is clear from various reports that glycoproteins of the plasma membrane which are electromobile have significant mobile fractions. Specific examples include Fc receptors on rat basophilic leukemia cells (Ryan et al., 1988) and concanavalin A receptors on *Xenopus* myotomal cells (Poo et al., 1979) which show mobile fractions of 0.7 and 0.5, respectively. Incorporated lipids dil and ganglioside G_{M1} are electromobile with a significant mobile fraction in *Xenopus* myotomal cells (Poo, 1981) although explicit values for the fractional mobility are not available in the literature.

According to Eq. (4) above, the surface potential that is relevant to the model proposed here is that due to surface charges within a Debye length of the membrane bilayer (see also Fig. 1). It is known for artificial membranes containing gangliosides with large anionic head groups that the total charge associated with the surface of the membrane is spread over a shell of ~25 Å thickness, well beyond the extent of the electrochemical double layer at normal physiological salt concentrations (McDaniel and

McIntosh, 1986; McDaniel et al., 1986). The effect on surface potential of such a spread of surface charge from the bilayer surface through the glycocalyx is discussed by Heinrich et al. (1982) for the erythrocyte. The extracellular surface potential they calculate corresponding to ψ_o in Eq. (6) above is in the range of -3 to -5 mV, a value much smaller than that expected if all charges are on the surface of the bilayer. A direct measurement of the shift in potassium conductance in squid axon upon shielding of surface charge by Ca^{+2} suggests that the surface potential near the bilayer in these membranes is of the order of -30 to -40 mV (Gilbert and Ehrenstein, 1969), although the charged groups producing this potential may be associated with the potassium channel protein. In neither of the above cases do the authors address the electrophoretic mobility of the cell-surface-associated charges responsible for the double layer potentials. Thus, based on literature values, it is difficult to ascertain the contribution of redistribution of surface charge toward the change in V_m in a particular cell exposed to an electric field. However, as can be seen in Fig. 3 *a*, the surface charge mediated reduction in induced V_m is 15% for a surface potential of only -3 mV, if all the charge generating that potential is mobile; this value rises to 23% for $\psi_o = -5$ mV. The membrane macromolecules which could contribute most effectively to surface charge effects discussed here are the negatively charged phospholipids phosphatidyl serine (PS) and phosphatidyl inositol (PI) which are more prevalent in the inner leaflet of the plasma membrane (Op den Kamp, 1974). However, even for cells with only a small fraction of the external face of the plasma membrane occupied by charged phospholipids, a significant electrophoretic redistribution effect is expected since membrane phospholipids exhibit large fractional mobility in general (Webb et al., 1981).

One important role this surface charge redistribution effect could play relates to cells or tissues in which long-term external electric field exposure is thought to provide an influence. Such biological systems include those of developing eggs and embryos (Jaffe, 1979; Overall and Jaffe, 1985), regenerating tissues (Borgens et al., 1977, 1981; Jaffe and Poo, 1979), and tissues under artificial stimulation for repair (Bassett et al., 1964; Kenner et al., 1975; Brighton and Pollack, 1984). If the change in V_m due to the extracellular electric fields plays any role in the mediation of the biological response, then one must consider the effects of surface charge redistribution. For example, a unidirectional extracellular field present for a time of the order of the surface charge redistribution time might well produce a more-or-less biphasic change in V_m due at first to the direct effect of the field and then, when the extracellular field intensity drops, to the residual effect of the (relaxing) redistributed surface charge.

The magnitude of endogenous electric fields in cells or tissues varies greatly between cell systems. Voltage gradients in regenerating newt limb stumps imply extracellular electric fields of at least 4 V/cm, and likely higher (McGinnis and Vanable, 1986). Robinson (1985) notes that electric fields emanating from wound sites are also of this order of magnitude. Even larger endogenous electric fields may be associated with the giant marine alga *Acetabularia* (Bowles and Allen, 1986), for which a large inward electric current density was found at the rhizoid. Overall and Jaffe (1985) reported large electric currents associated with *Drosophila* eggs sufficient to generate several millivolts of potential across the egg surface. Corn coleoptiles may develop voltage gradients of 80 mV across themselves (Grahm, 1964; Johnsson, 1965; Woodcock and Hertz, 1972). Thus, as can be seen in Fig. 4, the contribution of surface charge redistribution to changes in V_m could play a role in the responses of cells to endogenous current even at field strength down to a few volts per centimeter.

The redistribution of intracellular surface charge by endogenous electric fields may play a role in cellular response. In at least one case, a large electric current driven by ion pumps in the nurse cell anterior end of the oocyte follicle of the moth *Hyalophora cecropia* is thought to flow through a cytoplasmic bridge between the developing oocyte and the nurse cells (Jaffe and Woodruff, 1979). The resulting intracellular electric field is directed from oocyte to nurse cells across the bridge; the field orientation would tend to hyperpolarize the posterior oocyte end of the follicle and depolarize the anterior end via the surface charge redistribution effect. As the anterior end is the location of the current-generating ion pumps, it is conceivable that a V_m-mediated regulatory feedback system could operate via mobile intracellular surface charge.

A second situation in which intracellular electric fields and redistributing surface charge could play a role in the mediation of bioelectric responses of cells is wound repair. Consider cells very near the site of a wound which are exposed to the wound-associated electric field of 4 V/cm (McGinnis and Vanable, 1986). If the cells at this location are themselves damaged, the resistivity of their plasma membranes is low, i.e., $\lambda_m \sim \lambda_o \sim \lambda_i$ such that $f_\theta = 0, f_\beta = f_i = 2/3$. Thus, by Eqs. 2, 3, and 4 the direct effect of the endogenous electric field on V_m is zero while the effect due to redistribution of surface charge is still large. Assuming an outer surface potential of -5 mV and an inner surface potential of -50 mV, a 10 μm radius spherical cell membrane would be hyperpolarized on one side by 5 mV from -45 mV resting potential to -50 mV while the opposite side would be relatively unchanged. If the cell radius or the field strength is five times larger, the size of the hyperpolarization increases from -50 to -69 mV while that of the depolarization on the opposite side of the cell increases by 4 mV. It is feasible that endogenous wound currents might allow injured cells to repair by promoting the repolarization of at least a portion of the cell plasma membrane.

In summary, the proposed mediation of membrane potential changes due to redistribution of membrane surface charge appears to be of sufficient magnitude that it

could play a role in the modulation of V_m in cells exposed to endogenous or exogenous electric fields of the order of magnitude of those described in the literature.

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