ELECTROSTATIC MODELING OF ION PORES

II. Effects Attributable to the Membrane Dipole Potential

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ABSTRACT This paper presents calculations of the shielded dipole potential in the interior of a pore piercing a lipid membrane that is at a potential V_0 with respect to the aqueous solution. Except in the case of long narrow pores, there is substantial shielding of the membrane dipole potential. The associated dipole field never extends a significant distance into the aqueous region. The fact that the single-channel conductance of gramicidin B is only twice as large in glyceryl monooleate membranes as in phosphatidyl choline (PC) membranes, even though PC is ~120 mV more positive with respect to water, is interpreted in terms of the potential energy profile calculated for a gramicidin-like channel. It is demonstrated that the membrane dipole potential can significantly affect channel conductance only if the pore is narrow and if the peak in the potential energy profile occurs in the pore interior.

INTRODUCTION

Some years ago it was noted that the single-channel conductance of gramicidin B is only marginally affected by changes in lipid composition (Bamberg et al., 1976). This is in marked contrast to the effect of lipid variation on carrier-mediated cation transport (Hladky and Haydon, 1973; Benz et al., 1977; Benz and Gisin, 1978) or on the transport of positively or negatively charged lipophilic probe ions (Benz and Läuger, 1977; Pickar and Benz, 1978). These latter experiments provide compelling evidence for the existence of a membrane dipole potential. Conductance measurements carried out with aqueous solutions of varying ionic strength (Hladky and Haydon, 1973) or with membranes of different thicknesses (Pickar and Benz, 1978) demonstrate a reproducible lipid-specific effect on carrier-mediated or lipophilic ion transport that is distinct from effects due to the ionic double layer or to membrane thickness.

Our knowledge of the molecular structure of the water-membrane interface is inadequate to formulate a molecular theory of the dipole potential (Haydon, 1975; McLaughlin, 1977). However, any or all of the following structural units could create such a potential difference between the water and the membrane: the polar head groups, the ester linkages to the glycerol moiety, and the water molecules at the surface. Although direct measurements of a dipole potential are thermodynamically forbidden (Guggenheim, 1929, 1930), the changes in the dipole potential caused by changes in lipid composition can be inferred from conductance measurements (Paltauf et al., 1971; Hladky and Haydon, 1973; Pickar and Benz, 1978). The differences may be as great as 200 mV, corresponding to factors of as much as 10^3 for monovalent ion conductance.

Measurements of the current-voltage characteristics of gramicidin B in glyceryl monoleate (GMO) and dioleoyl phosphatidylcholine (PC) membranes showed single-channel conductances roughly twice as large in GMO as in PC (Bamberg et al., 1976). Conductance measurements using carriers or lipophilic ions suggest that a PC membrane is ~120 mV more positive than a GMO membrane (Hladky and Haydon, 1973; Pickar and Benz, 1978). If such a potential difference existed within the pore, the single-channel cation conductance of gramicidin B in GMO should be ~100 times that in PC. Clearly, the channel conductance process is shielded from the full effects of the dipole potential.

This paper presents calculations of the electrical potential along the axis of a right cylindrical "pore" piercing a slab of "membrane" in response to a dipole potential within the membrane. The pore and the surrounding aqueous solution have the same dielectric constant, ϵ_1; the membrane is a uniform dielectric with $\epsilon_2 < \epsilon_1$. I find that, unless the channel is extremely long or if the dielectrics are similar, there is substantial shielding of the dipole potential within the pore. Consideration of the conductance process in a gramicidin-like channel clearly indicates why changing lipids have little effect upon the conductance of the pore.

THEORY

The Model

The electric field experienced by an ion at any point in an aqueous channel is found by superposing contributions from various sources: the

[1]Jordan, P. C. Unpublished calculations.

image field due to polarization charges induced at the electrical phase boundary; the electric field caused by application of a transmembrane potential; the field created by the diffuse double layer at the membrane-water interface; and the field due to the dipole potential within the membrane, etc. If cooperative phenomena may be ignored, e.g., the possibility that the presence of an ion within a pore alters the structure of the pore or of the surrounding dielectric, then the total electric field is the sum of the separate components. Previous studies show how to compute the image field and the field generated by an applied potential (Parsegian 1969, 1975; Levitt, 1978*a*; Jordan, 1982). This work focuses upon the dipole field.

Although there is unambiguous evidence for the existence of a dipole potential (Paltauf et al., 1971; Hladky and Haydon, 1973; Hladky, 1974; Andersen and Fuchs, 1975; Pickar and Benz, 1978), the molecular origin of the effect is still unclear (Haydon, 1975; McLaughlin, 1977). Varying either the head group or the aliphatic chain or replacing ester linkages by ether linkages causes substantial variation in the electrical properties of a membrane, changes that have been interpreted as reflecting differences in dipole potentials of as much as 200 mV. The dipolar orientation of any or all of the following moieties may produce the effects observed: the polar head groups, the ester linkages, and the water molecules at the membrane surface.

As a molecular picture is unavailable, I analyzed a model in which the dipole potential is created by a sheet of surface dipoles with uniform surface dipole density μ_0, as illustrated in Fig. 1. It is immaterial whether the dipoles are located in the membrane, in the water, or partially in each phase as long as μ_0 is adjusted to create a specified dipole potential, V_0, in regions of the membrane far away from the pore. The extreme cases are $4\pi\mu_0 = \epsilon_2 V_0$ (dipoles within membrane) and $4\pi\mu_0 = \epsilon_1 V_0$ (dipoles in water phase). Whatever initial conditions are used, the physical picture remains the same. The dipoles at the membrane-water interface induce compensating charges along the pore-water boundary; these serve to partially screen the channel interior from the membrane. The dipole potential within the pore is thus less than V_0.

The Mathematics

A general method for calculating the electric potential within a channel in response to any source term has previously been described (Levitt, 1978*a*; Jordan, 1982). Its use requires determining a source potential. For the geometry of Fig. 1, the bare potential due to the surface dipoles is

$$\psi(z,r) = V_0[I(\delta - z,r) + I(\delta + z,r)] \tag{1a}$$

$$I(\alpha,\beta) = \frac{1}{4\pi}\int_1^\infty dr\, r \int_0^{2\pi} d\phi \cdot [\alpha/(\alpha^2 + \beta^2 - 2\beta r\cos\phi + r^2)^{3/2}]. \tag{1b}$$

Distances are measured in units of pore radius; δ is the ratio of membrane half-width to pore radius. Evaluation of the integral shows that, as $\beta \to \infty$, and $I \to |\alpha|/2\alpha$ and therefore, that $\psi(z,r)$ limits properly at large r; it is V_0 inside the membrane and zero outside. The source potential induces surface charges at the electrical phase boundaries. The full potential can then be computed (Levitt, 1978*a*) by solving a substitute problem in which the system is described as a uniform dielectric with fictitious surface charges chosen to recreate the electric field discontinuity in the real system, situated along the phase boundaries.

The replacement surface charge density functions, Y_i, are defined by a set of inhomogeneous integral equations (Eqs. 3–6 of my previous paper [Jordan, 1982]). For the dipole problem, the basic equation is

$$Y_i(t_i) = g[F_i(t_i) + \int_1^\infty d\rho\rho Q_{i1}^+(t_i,\rho)Y_1(\rho) + \int_0^\delta d\zeta Q_{i2}^+(t_i,\zeta)Y_2(\zeta)], \tag{2}$$

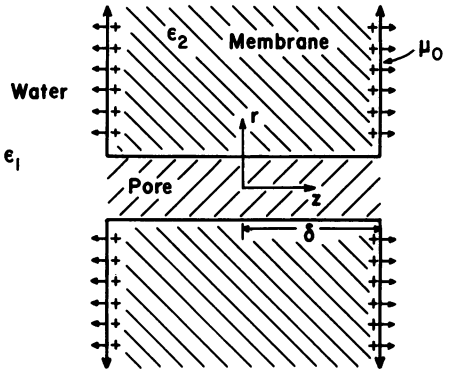

FIGURE 1 Cross-section of a cylindrical pore piercing a membrane slab of dielectric constant ϵ_2. The pore interior and the water are presumed to have the same dielectric constant, ϵ_1. Distances are scaled in terms of a unit pore radius. There is a uniform surface dipole density, μ_0, at the water-membrane interface that is the source of a dipole potential. The source strength is adjusted so that the potential in the membrane is V_0 far from the pore.

where $t_1 = r$, $t_2 = z$, and $g = (\epsilon_1 - \epsilon_2)/[2\pi(\epsilon_1 + \epsilon_2)]$. The kernels, Q_{ij}^+, are established by the system geometry. The inhomogeneous terms, F_i, are the normal components of the electric field generated by the source potential, Eq. 1, evaluated along the electrical phase boundary. Substantial algebra yields the simple expressions:

$$F_1(r) = V_0[J_1(2\delta,r) - J_1(0,r)],$$
$$F_2(z) = V_0[J_2(\delta - z,1) + J_2(\delta + z,1)] \tag{3a}$$

$$J_1(a,b) = \frac{1}{2\pi S}\left[K(\alpha) + \frac{1 - R^2}{T^2}E(\alpha)\right],$$

$$J_2(a,b) = \frac{a}{b}\left[J_1(a,b) - \frac{E(\alpha)}{\pi S T^2}\right] \tag{3b}$$

$$R^2 = a^2 + b^2,\ S^2 = R^2 + 2b + 1,$$
$$T^2 = R^2 - 2b + 1,\ \cos\alpha = T/S. \tag{3c}$$

$K(\alpha)$ and $E(\alpha)$ are complete elliptic integrals of the first and second kind, respectively (Abramowitz and Stegun, 1965).

The solution of Eq. 2, given the F_i of Eq. 3, is far from straightforward. In addition to the "corner singularities" in the Y_i, due to the geometry chosen (Jordan, 1982), there are additional complications, because the inhomogeneous terms are also singular where the pore cylinder pierces the membrane slab. As $r \to 1$ or $z \to \delta$, the leading terms in the F_i are

$$F_1 \sim \frac{V_0}{2\pi}\left[\frac{1}{r-1} + \frac{1}{2}\ln(r-1)\right],\ F_2 \sim \frac{-V_0}{2\pi(\delta - z)}. \tag{4}$$

It is possible to transform to new variables

$$x_1 = r - 1,\ x_2 = \delta - z,\ \xi_1 = \rho - 1,\ \xi_2 = \delta - \zeta, \tag{5}$$

and rewrite Eq. 2

$$\mathbf{Y}(x) = g[\mathbf{F}(x) + <\mathbf{Q}(x,\xi)\cdot\mathbf{Y}(\xi)>] \tag{6}$$

to explicitly determine the singularities in $\mathbf{Y}(x)$. The result is

$$\mathbf{Y}(x) = V_0\left[\mathbf{w}(x) + \mathbf{c} + \Omega(x)\cdot\mathbf{b} + \frac{\mathbf{a}}{x}\right] \qquad x < 1 \tag{7a}$$

$$\mathbf{Y}(x) = V_0\,\mathbf{w}(x) \qquad x > 1. \tag{7b}$$

The vectors **a** and **c** compensate for the singularities in **F** as $x \to 0$: $a_1 = -a_2 = 2g/(1 - \pi g)$ and $c_1 = -a_1/2, c_2 = -\frac{1}{2}$. The matrix $\Omega(x)$, defined earlier (Jordan, 1982), describes the corner singularities imposed by system geometry; **b** is adjusted so that $\mathbf{w}(x) \to 0$ as $x \to 0$. The method described previously can now be used to establish the unknown quantities $\mathbf{w}(x)$ and **b**. The results then determine the dipole potential along the pore axis.

The numerical calculations are not as rapidly convergent as are the image potential and electric field profile computations (Jordan, 1982). A substantially finer grid along the water-membrane interface is needed if 0.5% accuracy is to be attained. Stability is not assured unless $Y_1(r)$ is approximated at ~40 points (in the previous work only ~16 points were needed). No similar complication arises in the estimation of $Y_2(z)$; the grid spacings that were appropriate in the earlier work are also adequate here.

RESULTS AND DISCUSSION

General Features

The ratio of the dipole potential on the channel axis to that in the membrane interior, V/V_0, is plotted as a function of z/δ for a number of half-width to radius ratios, δ, in Fig. 2. For the cases illustrated, the dielectric ratio, $K \equiv \epsilon_1/\epsilon_2$ is 40, representative of a membrane-pore-water system. Even if $\delta = 25$, which is far larger than would be found in any channel of biological interest, there is nonnegligible shielding of the membrane dipole potential. For a gramicidin-like channel with $\delta \sim 7.5$, the dipole potential at the center of the pore axis is about half its value in the membrane.

Because the abscissa z/δ is equal to x/W, where x is the unscaled axial distance from the channel center and $W = L/2$ is the half-width of the membrane, Fig. 2 illustrates the effect that changing pore radius in a membrane of specified thickness has on the dipole potential. The potential profiles, particularly for the larger values of δ, clearly reflect the dipolar nature of the source. The potential remains close to its maximum value until near the channel mouth; it then falls off very sharply, almost to zero, away from the immediate vicinity of the membrane. Within the pore ($z < \delta$) shielding becomes less significant as δ increases. Just outside the channel mouth is a transition region in which the curves all cross, so that the larger the pore radius, the further the dipole potential extends into the aqueous solution bathing the membrane. Because this portion of the figure is confusing, an exploded view is plotted in the insert. Only for wide pores ($\delta \lesssim 2.5$) is the dipole potential in the aqueous region a significant fraction of its value inside the pore.

Fig. 2 illustrates how pore radius variation alters the dipole potential in a membrane of fixed thickness. A different perspective is obtained if the pore radius, a, is kept constant and the membrane thickness is varied. The potential near the channel mouth is replotted as a function of $z - \delta$ in Fig. 3; distance is measured in units of pore radius $z = x/a$. Because the curves are parallel for $z > \delta$, at least for the larger δ, the dipole field exterior to the pore becomes independent of the membrane width as W increases. If the membrane is sufficiently thick, the only variable affecting the dipolar field in the aqueous solution is the radius of the pore itself. This is what is expected qualitatively and provides further evidence of the reliability of the calculation.

Finally, it is possible to represent the dipole potential at

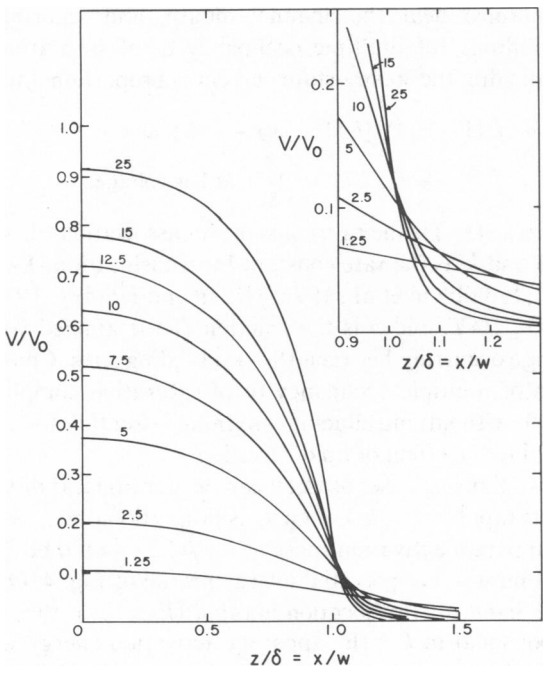

FIGURE 2 Shielded dipole potential, V/V_0, on the axis of a cylindrical channel as a function of the ratio of the distance from the membrane center to the membrane half-width, z/δ. Eight membrane half-width to pore radius ratios, δ, are illustrated. The insert in the upper right-hand corner is an exploded view of the potential near the channel mouth for six values of δ. In all cases, the dielectric ratio, $K = \epsilon_1/\epsilon_2$, is 40.

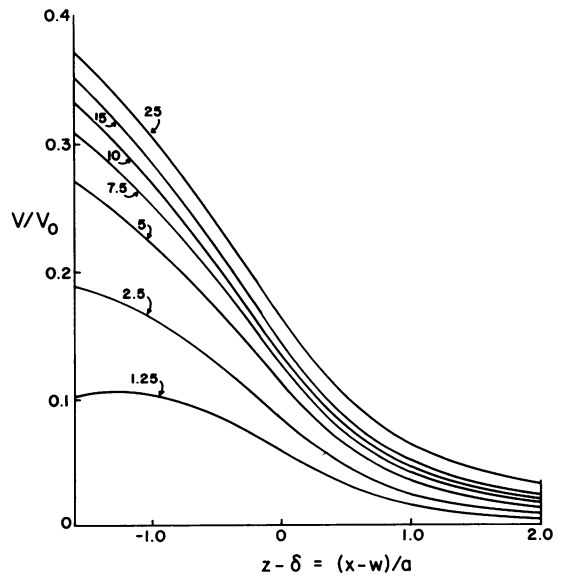

FIGURE 3 Shielded dipole potential, V/V_0, on the axis of a cylindrical channel as a function of the distance from the channel mouth, $z - \delta$. Seven δ values are illustrated; the dielectric ratio, K, is 40.

the center of the channel, $V^* = V(0)$, by an empirical expression

$$V^*/V_0 = 1 - \exp-[c_1\delta + c_2\delta^2], \quad (8)$$

that is accurate to better than 2% for $1.25 \leq \delta \leq 20$ for dielectric ratios >10. The values of c_i for a range of K's are given in Table I. If $K = 40$ or 80, then Eq. 8 is adequate for all $\delta > 1.25$.

Electrolyte Shielding

Because all calculations were carried out assuming the aqueous phase to be nonconducting (zero ionic strength), we should consider the significance of this approximation. Lifting this restriction and including effects due to electrolyte shielding can substantially affect the potential profile only if the potential penetrates at least two Debye lengths into the aqueous region. If the pore is wide enough ($\delta \sim 2.5$), as may be the case in porin (Benz et al., 1978; Benz et al., 1979), such penetration is significant at high ionic strength (Jordan, 1982). The shape of the dipole potential would be altered in the surrounding electrolyte. Although the profile must be changed in this case, this only slightly affects the total energy barrier to ion passage through the pore because the absolute effect is minimal. Given an ionic strength of 1 M and a membrane width of 3.0 nm, the residual dipolar potential two Debye lengths (0.6 nm) from the channel mouth is only 2.5% of its value in the membrane for $\delta = 2.5$. Because membrane-dipole potentials are no greater than 500 mV (Andersen and Fuchs, 1975), electrolyte shielding in this instance only modifies the field in a region where the dipole potential change is 10–15 mV. The consequences of such variations are too small to be significant. Thus, electrolyte shielding leads to no quantitatively important changes in the dipole potential, regardless of the value of δ.

Gramicidin B

The effect of lipid variation on single-channel conductance in gramicidin B can be understood by considering a kinetic model for the process of ion flow. This, and the underlying potential energy profile, are illustrated in Fig. 4. There are five basic steps: diffusion to and from the channel mouth; association and dissociation at binding sites near the entrance to the channel; translocation from one binding site to the other (Läuger, 1973; Sandblom et al., 1977; Levitt, 1978*b*; Urban and Hladky, 1979; Andersen and Procopio, 1980; Finkelstein and Andersen, 1981). Although an oversimplification, the model accounts for those features of the conductance process essential in interpreting the lipid variation experiments.

TABLE I
VALUES OF THE PARAMETERS C_1 AND C_2, WHICH CHARACTERIZE THE CURVE FITTING FUNCTION, EQ. 8, FOR VARIOUS DIELECTRIC RATIOS K

K	C_1	C_2
10	0.30506	−0.006041
20	0.17183	−0.001126
40	0.08982	+0.000878
80	0.04485	+0.001225

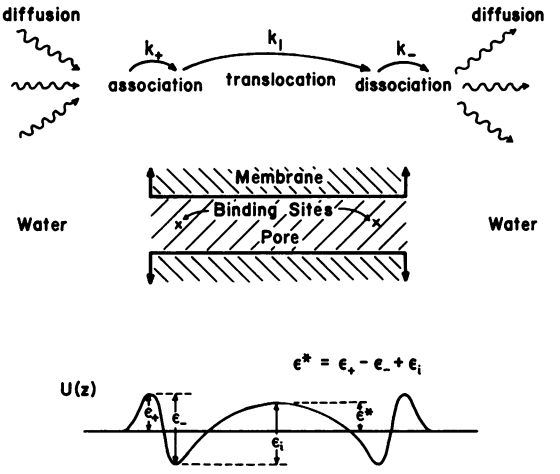

FIGURE 4 Schematic model for ion translocation through a gramicidin channel. *Top:* illustration of the five separate steps with their associated rate constants. *Middle:* model of the pore indicating the position of the binding sites. *Bottom:* potential energy profile with the associated energy barriers. Local variations in the potential energy have been smoothed.

Assuming that diffusion in the aqueous electrolyte is rapid enough so the equilibrium cation concentration is maintained near the channel mouth, and ignoring the possibilities of multiple occupancy or of saturating the gramicidin, the steady-state current is proportional to

$$J_{ss} \alpha k_+ k_i (1 - e^{-\psi})/[k_i(1 + \omega^2) + k_-\omega], \omega \equiv e^{-(1+a)\psi/4} \quad (9a)$$

$$\alpha k_+ k_i \psi/(k_- + 2k_i), \text{ at low voltage,} \quad (9b)$$

where $k_+(k_-)$ is the rate constant for association (dissociation) and k_i is the rate constant for translocation (Läuger, 1973; Sandblom et al., 1977; Urban and Hladky, 1979); ψ is zeV_{app}/kT, and a is the fraction of the applied voltage change occurring between the two binding sites. Consideration of multiple occupancy or of saturation complicates Eq. 9 without introducing anything essential to understanding the effect of lipid variation.

Two limiting cases of Eq. 9 can be identified. If dissociation is rapid ($k_- \ll k_i$), then J_{ss} is proportional to k_+k_i/k_-; the apparent activation energy for ion flow would be ϵ^*, the maximum in the potential energy profile of Fig. 4. On the other hand, if translocation is rapid ($k_i \gg k_-$), then J_{ss} is proportional to k_+; the apparent activation energy would be ϵ_+, the energy barrier at the entrance to the channel.

The experiments contrast the single-channel conductance of gramicidin B in membranes formed from PC with ones formed from GMO (Bamberg et al., 1976). Measurements of carrier-mediated cation conductance (Hladky and Haydon, 1973) and lipophilic ion conductance (Pickar

and Benz, 1978) strongly suggest that the differences between the electrical properties of PC and GMO reflect that PC is ~120 mV more positive than GMO. Assuming that the structure of the gramicidin channel is the same in PC and GMO, then the conductance differences should be interpretable in terms of the effective dipole potential within the pore.

In order to apply the theory, considering the effect of lipid variation on single channel conductance in gramicidin-B, it is necessary to estimate the parameter δ for a gramicidin-like channel. The length of the channel is ~2.6 nm and its diameter is ~0.43 nm (Koeppe et al., 1978). However, the thickness of a lipid bilayer membrane formed from C_{18} phospholipids varies from 3 to 5 nm, depending upon the solvent (Benz et al., 1975). Thus, there is likely to be curvature of the membrane surface where it attaches to the channel mouth. As a result, the effective length of a channel, incorporated into a membrane, is greater than its actual length. Furthermore, the gramicidin molecule is not electrostatically equivalent to lipid. Measurements on the polypeptide $(Gly\text{-}Ala)_n$ (Tredgold and Hole, 1976), which is similar to gramicidin in that none of the amino acids has a polar residue, suggest that a dielectric constant of ~4 is appropriate to crystalline gramicidin (Levitt, 1978*a*). The higher dielectric constant region formed by gramicidin partially shields the pore interior from the full effect of the membrane dipole potential so that, in terms of the two dielectric model, the effective pore radius is a bit greater than the physical pore radius.

Although the calculations presented here can be modified to account for both curvature at the channel mouth and dielectric dissimilarity between gramicidin and lipid,[1] the necessary changes are not computationally simple. To incorporate a realistic membrane width yet still maintain the idea of a straight-sided channel, I have chosen to describe the assembly near the pore as being equivalent to a system 3.0-nm wide. If the pore is incorporated into a solvent-free region, this value is reasonable. If it is in a thicker part of the membrane, there must be substantial flaring at the channel mouth; however, the narrow part of the assembly cannot be much wider than 3.0–3.5 nm.

The effect of shielding on the image potential for an ion in a gramicidin-like dielectric has been analyzed for infinite channels (Jordan, 1981); the results can be used to bound the image potential for an ion in a finite channel. For a 3.0-nm channel with gramicidin's physical and electrical properties, the peak in the electrical image barrier is between 24 and 28 kJ mol^{-1}. When the results of previous work (Jordan, 1982) are applied, these energies suggest that an effective pore radius of 0.24–0.26 nm is appropriate for an assembly described as a straight-sided pore separating two dielectric phases. The effective value of δ for a gramicidin-like channel is therefore between 5.75 and 6.25.

For a gramicidin-like channel with $\delta \sim 6$, it is clear from Fig. 2 that the dipole potential at the center of the channel is about half its value in the membrane. Near the pore mouth, where the entrance barrier is located, it is between one-fifteenth and one-fourth of the membrane value, depending on the precise location of the peak. The consequences for the potential barrier and the conductance of gramicidin-like pores in GMO and PC membranes are contrasted in Table II for δ values ranging between 5.75 and 6.25. If translocation across the central barrier is rate-limiting, then conductance in GMO should be ~7–8 times that in PC. If the barrier to entering the channel is more important, then the conductance ratio should be ~1.4–2.7. The experimentally determined ratio is ~2 (Bamberg et al., 1976), corresponding to the second possibility. As long as translocation is faster than dissociation, as was found experimentally (Urry et al., 1980; Andersen and Procopio, 1980), then changing lipids can only slightly alter the single-channel conductance of gramicidin. The slow step in this kinetic process takes place near the channel mouth, a region where the dipolar potential within the pore is decreasing rapidly. As a consequence, the lipid specific effect is essentially eliminated.

It is now evident why the complications of multiple occupancy do not have to be considered in discussing the lipid variation experiments. Inclusion of this possibility multiplies the denominator of Eq. 9b by the term $(1 + 2K_2c)$, where K_2 is the binding constant for a site when the other is already occupied, and c is the bulk cation concentration. Since K_2 is the equilibrium constant for a process occurring at the channel mouth, it is also insensitive to changes in the membrane dipole potential and cannot cause major lipid specific effects. If there is saturation, the situation is analogous although for different reasons. The kinetics are governed by competition between dissociation and diffusion (Andersen, 1983) both of which occur near the channel mouth where the dipole potential is small.

TABLE II
COMPARISON OF DIPOLE POTENTIAL DIFFERENCES AND CONDUCTANCE RATIOS FOR MONOVALENT CATION TRANSPORT THROUGH GMO AND PC MEMBRANES

	Carrier (Haydon and Hladky, 1973)	Gramicidin-like channel, potential peak at	
		Channel center	Channel mouth
$(\Delta\phi^{PC}\text{-}\Delta\phi^{GMO})$/mV	115	~48–52	~ 8–25
$\Lambda^{GMO}/\Lambda^{PC}$	~100	~7–8	~1.4–2.7

The entries refer to carrier-mediated transport and to transport through a gramicidin-like channel. For channel transport the differences attributable to changing the position of the peak in the potential profile are contrasted. $\Delta\phi$ is the dipole potential at a point within the membrane relative to a point in the aqueous phase far removed from the surface of the membrane. Λ is the equivalent conductance. At the channel center the range of values is a consequence of varying δ between 5.75 and 6.25. At the channel mouth the range is a consequence of varying the position of the peak in the potential profile.

Other Systems

As the discussion of the gramicidin B-GMO and -PC systems indicates, differences in membrane dipole potential can substantially alter channel conductance only if two conditions are met (*a*) the channel is sufficiently narrow ($\delta \gtrsim 5$) and (*b*) the maximum in the total potential energy occurs in the pore interior. Unfortunately, few systems satisfy both conditions. The interior sections of the pores formed by excitability-inducing material (Latorre et al., 1972), haemocyanin (Latorre et al., 1975; McIntosh et al., 1980), and porin (Benz et al., 1978; Benz et al., 1979) may be too wide, regardless of their structure.

Gramicidin would be ideal if the barrier near the channel mouth were lower. This could be accomplished by inserting the pore into negatively charged membranes like phosphatidyl serine or phosphatidyl glycerol. Whether there would be dramatic differences depends upon how much the entrance barrier is lowered and if a negatively charged pair of lipids with significantly different dipole potentials could be found.

The alamethicin channel has complicated conductance characteristics, largely a reflection of the kinetics of channel formation (Eisenberg et al., 1973; Boheim and Kolb, 1978; Kolb and Boheim, 1978). In its lowest conductance state, the channel appears to be narrow (Hanke and Boheim, 1980). Furthermore, there seem to be differences between alamethicin's properties in GMO and in PC (Latorre and Alvarez, 1981). Experiments that focus upon the consequences of lipid variation may establish which channel properties are specifically sensitive to changes in the dipole potential, thereby determining some of the characteristics of the channel interior.

Monazomycin presumably forms its channel by the parallel alignment of five monomer units (Muller and Finkelstein, 1972). Since little is known about the interior structure of the pore, lipid variation studies may provide information.

It would be especially interesting to carry out lipid variation experiments on biological channels. This requires successful insertion procedures. Once this is accomplished, changing the dipole potential provides another tool for probing the channel structure.

For the potassium channel from sarcoplasmic reticulum, dramatic effects should not be observed if the model proposed by Miller (1982) is correct. From blocking studies it appears that the narrow portion of the channel is only ~1.0 nm long with a radius of ~0.25 nm at its thinnest point (Coronado and Miller, 1982; Miller, 1982); as a result, $\delta \sim 2$, and no large dipole potential related effects are expected. If any are found it would strongly suggest that, in addition to its short, narrow portion, the channel widens out only slightly over a substantial distance.

The biological channel in which lipid variation may lead to substantial effects is in the potassium channel from squid giant axon, presumed to contain a long, narrow segment (Hodgkin and Keynes, 1955; Adelman and French, 1978). Such studies await the development of successful insertion procedures.

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