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The Gating Currents of Sodium Channels: Pore-Population-Size Effects

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Sodium-channel behavior has been modeled in order to determine the answer to the following question: How large must a population of "on-off" sodium pores be before the inherently random behavior of the individual channels becomes smoothed to yield the expected gating current-conductance relationships which would be predicted from an infinite pore array? Results of this analysis show that for the "opening" situation, an excellent fit was obtained whenever more than about 10 pores were considered. Significant discrepancies were observed in the "closing" situation, however, for pore arrays of 50 or less. Marked hysteresis is apparent in the behavior of small pore populations.

Key words: gating currents, sodium channels, pore populations

INTRODUCTION

In their original presentation of the now classic Hodgkin-Huxley (H-H) hypothesis, these authors noted that observed changes in sodium and potassium conductance of nerve could be conceptualized as resulting from either 1) change of diameter in a fixed number of ion-selective membrane channels, or 2) from change in the proportions of these channels in a) "open," conducting, and b) "closed," nonconducting, states (1). Although the first concept contains the attractive element that, for example, all sodium pores could be considered to be in the same condition at the same time, it unfortunately also requires that pore selectivity [which apparently is fixed (2)] be maintained over a wide range of pore diameters. Hodgkin and Huxley, as well as later workers have, therefore, appeared to favor the second of these conceptualizations. Subsequently, evidence from studies of conductance "noise" in different excitable membranes (3, 4) has added strong support for the essentially "on-off" nature of individual conductance channels.

It follows, then, that there must be a necessary distinction between the behavior of individual channels and the behavior of the membrane as a whole. How large must a population of pores be before the inherently random behavior of the individual channels becomes smoothed to yield the expected relationships which would be predicted from an infinite pore array?

In seeking an analytical answer to this question, we chose to consider changes in "activation" of Na^+-selective channels as controlled by the m variable of the H-H equations.

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Where h, the "inactivation" variable, is ignored:

$$\frac{dg_{Na}}{dt} = \frac{dg_{Na}}{dm} \cdot \frac{dm}{dt} \tag{1}$$

The fundamental relationship, dg_{Na}/dm, can thus be studied separately from the time-dependent process dm/dt. If we further state that it is only f, the fraction of pores in the open state, which truly concerns us, then:

$$\frac{dg_{Na}}{dm} = \frac{df}{dm} \tag{2}$$

where both f and m are simple functions varying between 0 and 1.

For an infinite pore array, the H-H formulation makes clear that f must always be equal to m^3, m being obtained from the kinetic relationship:

$$m' \underset{\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} m \tag{3}$$

in which α_m and β_m are voltage-dependent rate constants. By contrast, for a single, isolated "on-off" pore (a 1-pore array), we can readily see that f is not equal to m^3 at all values of m. For such a pore to open, all 3 of its controlling "particles" must be in the m rather than the m′ state. Thus as m rises from 0 to 0.33, 0.67, and 1, f remains 0 until m reaches 1. [Note that when m = 0.67, f is still 0, not $(0.67)^3$.]

The original question thus becomes: How large must the array of pores be before f comes to approximate m^3 at all values of m?

METHODS

The simplest model for the behavior of small pore arrays (up to n = 13, where n is the number of pores in the array) can be obtained by utilizing a deck of playing cards with 1 suit removed. The triplets with the same face value then represent the 3 m-gates associated with a single sodium pore. When the cards have been thoroughly and carefully shuffled, the f:m relationship can be studied either for pore opening (cards are dealt until full triplets are obtained, m = fraction of cards dealt, 1–f = fraction of triplets obtained) or for pore closing (m′ = fraction of cards dealt, 1–f = fraction of pores closed, remembering that a pore is closed by the laying down of a single card from each potential triplet).

To verify results obtained by this method and to study larger pore arrays than can conveniently be modeled by direct methods, a probabilistic model was developed for computer use. We modeled only the pore-closing situation in this way, however, since for the pore-opening situation f rapidly approaches m^3 as n is increased, and becomes essentially equal to m^3 at all times, even in a 13-pore array.

For pore-closing, the question was posed in the form: How many gates are required to change from the m to the m′ condition in order to close j pores? Our basic approach involved recognition that at any stage during the closing process, gates and pores may be separated into 3 subpopulations: firstly, the j–1 pores already closed by either 1 or more m to m′ transitions; secondly, the single jth pore which will be next to close by a single such m to m′ transition; and finally, there are those remaining gates (in the m state) associated with either open or closed pores. Where q is the number of additional m to m′ transitions possible with respect to the already closed j–1 pores, and where r is the number of pores in this first subpopulation closed by 3 gates in the m′ state, then the number of gates, E(j,n), required to close j pores is given by the following equation:

$$E(j,n) = \frac{3^j n!}{(3n)! \cdot (n-j)!} \sum_{q=0}^{2j-2} (j+q)! \cdot [3n-(j+q)! \cdot \sum_{r=0}^{j-1} [r!\,(q-2r)!\,(j-1-q+r)!]^{-1}\, 3^{-r} \qquad (4)$$

In equation 4, $E(j,n) \equiv (1-m) = m'$, while $f = j/n$.

RESULTS

Results of this analysis are shown in Fig. 1. In this figure, the solid curve represents the f–m relationship predicted from the infinite pore array, namely $f = m^3$. For the "opening" situation (i.e., increasing m, increasing f), an excellent fit was obtained wherever n was greater than about 10 pores. Significant discrepancies were observed in the "closing" situation, however, for pore arrays of 50 or less. Marked hysteresis is apparent in the behavior of small pore populations.

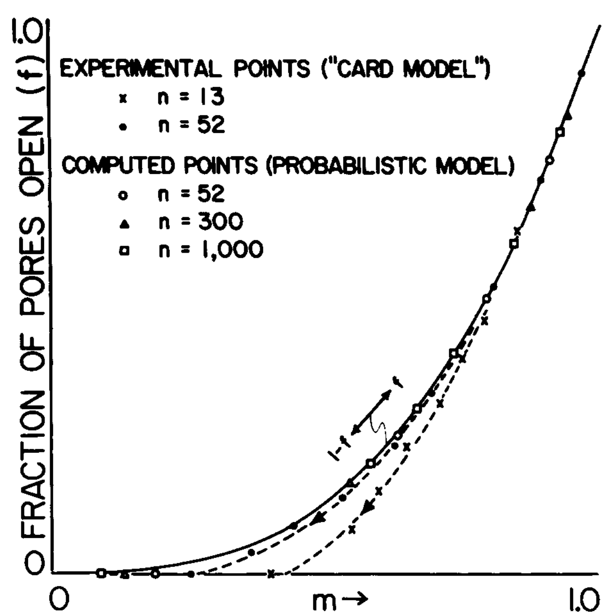

Fig. 1. Gating current-conductance relationships for pore populations of various sizes. The solid curve refers to an infinite pore array; the curve reflects both the opening (f) and closing (1–f) of sodium pores as a function of m-gate transitions (m′ to m, and m to m′, respectively). The dashed lines refer to small pore populations; these curves reflect only the closing of sodium pores as a function of m-gate transitions (m to m′). See text for further discussion.

DISCUSSION

The analysis presented here was undertaken, initially, because we had suspected that discrepancies between predicted results (from H-H equations) and observed sodium tail currents and associated gating currents (5–7) might perhaps arise from pore-population-size effects, i.e., from hysteresis of the type observed for very small pore arrays in Fig. 1. It is very clear that this could not be the case. In fact, there must be very few situations in which sufficiently small pore arrays could be encountered experimentally to produce hysteresis as a result of population size.

It is interesting to note, however, that the "kinetic formulation" of the H-H equations, as modified initially by Bezanilla and Armstrong (8), and more extensively by Moore and Cox (9), superimposes on the original H-H formulation just such a hysteresis between pore opening and pore closing as we had sought to uncover in this study.

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REFERENCES

1. Hodgkin, A. L., and Huxley, A. F., J. Physiol. 117:500 (1952).
2. Chandler, W. K., and Meves, H., J. Physiol. 180:788 (1965).
3. Anderson, C. R., and Stevens, C. F., J. Physiol. 235:655 (1973).
4. Begenisich, T., and Stevens, C. F., Biophys. J. 15:843 (1975).
5. Bezanilla, F., and Armstrong, C. M., Science 183:753 (1974).
6. Armstrong, C. M., and Bezanilla, F., J. Gen. Physiol. 63:533 (1974).
7. Keynes, R. D., and Rojas, E., J. Physiol. 239:393 (1974).
8. Bezanilla, F., and Armstrong, C. M., Phil. Trans. R. Soc. Lond. B 270:449 (1975).
9. Moore, J. W., and Cox, E. B., Biophys. J. 16:171 (1976).