BRIEF COMMUNICATIONS

COMPUTATION OF AXON GATING CURRENTS FROM DIPOLE MOMENT CHANGES IN CHANNEL SUBUNITS

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ABSTRACT The gating polarizational currents were computed on the basis of the dipole moment changes occurring in nerve membrane ionic channel subunits. Membrane thickness and surface density of channels were the only parameters used in addition to the Hodgkin-Huxley model. The gating currents computed for membrane potentials where the Hodgkin-Huxley empirical formulae are reliable were found to be in good agreement with the available experimental data. It is demonstrated that the gating currents of the n and h subunits are responsible for the late slowly decaying gating currents.

The existence of functional structural units which respond to electric fields and thereby control the ionic permeability of nerve membranes, arises almost inevitably from the idea of specific channels in nerve membranes. Within the Hodgkin-Huxley axon model framework, these are the n, m, and h units. Each of these units can be in either one of two possible states (configurations) which must differ in their electrical properties in such a way that the membrane electric field controls both the kinetics of the transitions from one state to another and the equilibrium distribution. Therefore, if we assume that these functional units are electrically insulated from the membrane matrix, they must generate polarization displacement currents across the membrane when changing their states in response to external electrical fields.

In 1952 Hodgkin and Huxley (1) predicted the existence of these currents which were later called "gating currents." However, their measurement turned out to be so difficult that they were first detected only in 1973 (2, 3). Recently, Levitan and Palti (4) computed the changes in the dipole moments of the gating units (m, n, and h) on the basis of the empirically determined voltage dependence of the membrane conductance rate constants. They also argued that if one assumes that the above changes in the electric properties of the gating units reduce to dipole moment changes, one can compute the gating currents from the dipole moment changes.

It is the object of this work to compute the axon gating currents on the basis of the dipole moment changes and compare the results with the available experimental evidence (5–7). Within this framework the gating current component generated by the changes of the i-gating units, $j_{g(i)}$, is given by the corresponding polarization displacement current:

$$j_{g(i)} = \partial P_i/\partial t = K_i N_i \Delta M_i (\mathrm{d}X_i/\mathrm{d}t)/\delta, \tag{1}$$

where i denotes the type of gating unit ($i = n$, m, and h in the Hodgkin-Huxley axon model) and the corresponding type of channel; P_i, the dielectric polarization of the gating unit system; K_i, number of gating units of type i per channel; N_i, the number of channels per unit membrane area; ΔM_i, dipole moment change occurring when one i-gating unit is converted from "closed" to "open" state; X_i, the fraction of i-gating units in the "open" state; δ, membrane thickness.

Eq. 1 can be rewritten by substituting the solutions of the differential equations for X_i for a potential step (1):

$$j_{g(i)} = K_i N_i \Delta M_i (X_{i\infty} - X_{i0}) \exp(-t/\tau_i)/(\tau_i \delta), \tag{2}$$

where X_{i0} and $X_{i\infty}$ are the values of the function X_i just before and an infinite time after the potential step; τ_i is the time constant of the exponential change of X_i after the potential step.

In accordance with the experimental procedure (5, 8) we will deal with positive and negative potential steps (external electrode serving as a reference) of magnitude ΔE. The potential steps may be either from a holding potential, E_0 (turn-on) or from potentials $E_\pm = E_0 \pm \Delta E$ to E_0 (turn-off). The experimentally determined quantity is in both cases the so-called asymmetric gating current $\Delta j_{g(i)}$ which equals the algebraic sum of the gating currents originating from a pair of potential steps in opposite directions:

$$\Delta j_{g(i)} = j_{g(i)}{}^{+} + j_{g(i)}{}^{-}. \tag{3}$$

The notation + corresponds to the membrane potential E_+, – to E_-, and 0 to E_0.

From Eq. 2 and 3 we get for both turn-on and turn-off cases, the following relationships:

$$\begin{aligned} \Delta j_{g(i)}^{(\text{turn-on})} = {} & K_i N_i/\delta\,[\Delta M_i{}^{+}(X_{i\infty}{}^{+} - X_i^0) \exp(-t/\tau_i{}^{+})/\tau_i{}^{+} \\ & + \Delta M_i{}^{-}(X_{i\infty}{}^{-} - X_i^0) \exp(-t/\tau_i{}^{-})/\tau_i{}^{-}], \end{aligned} \tag{4}$$

$$\Delta j_{g(i)}^{(\text{turn-off})} = K_i N_i \Delta M_i^0/\delta (2X_i^0 - X_{i\infty}{}^{+} - X_{i\infty}{}^{-}) \exp(-t/\tau^0)/\tau^0. \tag{5}$$

Since ΔM_i can be calculated (4) by means of Eqs. 4 and 5 one can compute the asymmetric gating currents for a variety of conditions and compare the results with the experimental evidence. Note that the above derivations are based on the assumption that the time interval between two consecutive steps is considerably greater than the duration of all the corresponding transients.

In the computations of the parameters appearing in Eqs. 4 and 5, the empirical formulae of Hodgkin and Huxley for the squid and Frankenhäuser for the frog were used (9, 10). The only additional parameters needed in Eqs. 4 and 5 are the membrane thickness which was assumed to be 75 Å, and the number of channels per unit area of membrane surface. This value was taken as 400 μm^{-2} both for sodium and potassium channels for the squid and 4,000 μm^{-2} for the frog.

The computed as well as the experimental asymmetric gating currents are presented in Figs. 1–4. The figures illustrate the gating currents generated by each type of Hodgkin & Huxley kinetic units (*m*, *n*, and *h*) separately as well as their sum. It should be noted here that in all four cases presented the potentials $E_- = E_0 - \Delta E$ correspond to a very deep hyperpolarization with τ^- close to zero. Under these conditions the

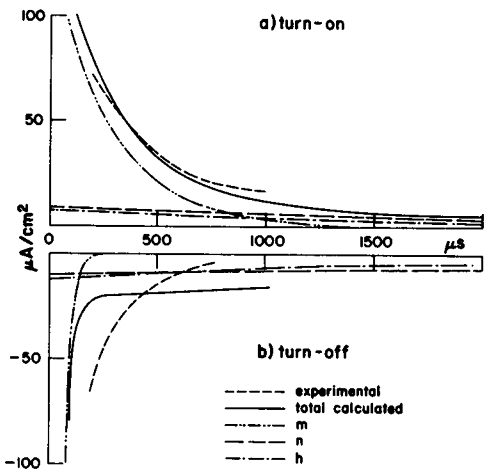

FIGURE 1

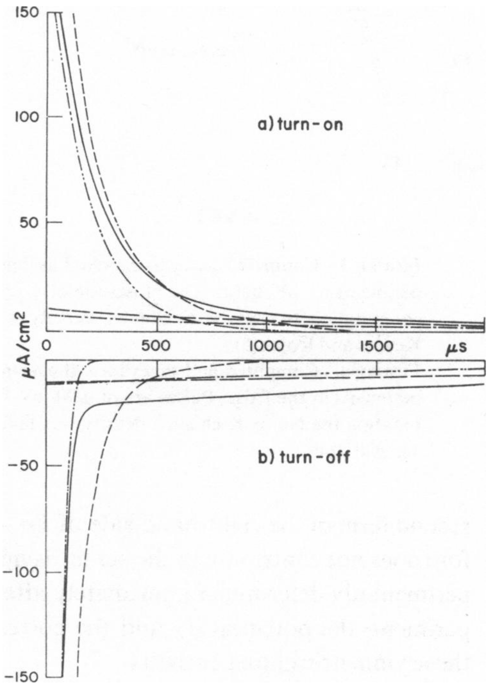

FIGURE 2

FIGURE 1 Computed and experimental asymmetric gating currents for turn-on and turn-off experiments in the squid. Pulses are of ±100 mV from a holding potential of −103 mV. In the computation the Na or K channel density was taken as 400 μm^{-2}. Experimental data from Rojas and Keynes (7).

FIGURE 2 Computed and experimental asymmetric gating currents for turn-on and turn-off experiments in the squid. The pulses are of ±120 mV from a holding potential −100 mV. In the computation the Na or K channel density was taken as 400 μm^{-2}. Experimental data from Keynes and Rojas (5).

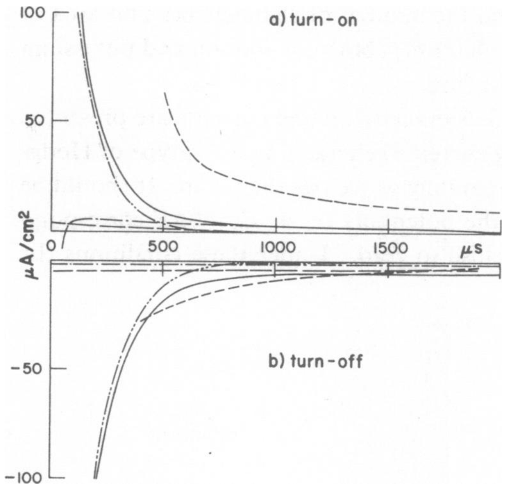

FIGURE 3

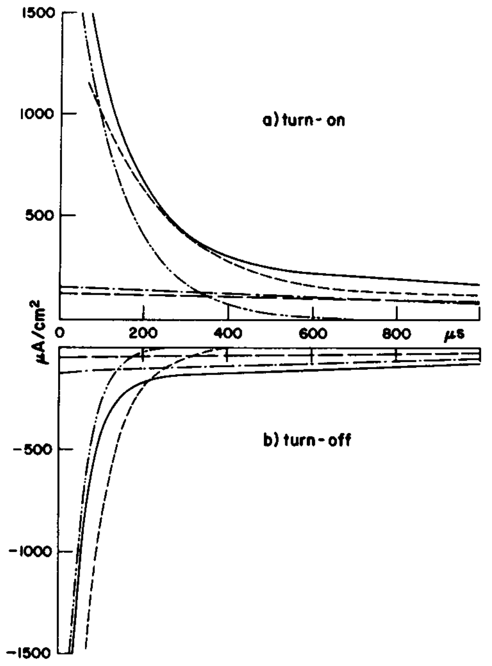

FIGURE 4

FIGURE 3 Computed and experimental asymmetric gating currents for turn-on and turn-off experiments in the squid. The pulses are of ±120 mV from a holding potential −70 mV. In the computation the Na or K channel density was taken as 400 μm^{-2}. Experimental data from Keynes and Rojas (5).

FIGURE 4 Computed and experimental asymmetric gating currents for turn-on and turn-off experiments in the frog. Pulses are of ±90 mV from a holding potential −113 mV. In the computation the Na or K channel density was taken as 4,000 μm^{-2}. Experimental data from Nonner et al. (6).

second term of the right-hand side of Eq. 4 approaches a Dirac δ-function, and therefore does not contribute to the actual asymmetric gating currents which can not be experimentally determined immediately after the potential step. Thus, for turn-on experiments the potential E_+ and the corresponding time constant τ^+ alone determine the asymmetric gating currents.

The figures illustrate that under some conditions the computed results are in good agreement with the experimental data, while in others the agreement is only fair. However, note that the calculated results which correspond to membrane potentials for which the empirical formulae used are reliable (cases *a* in Figs. 1, 2, and 4 and case *b* in Fig. 3) are in best agreement with the experimental results.

The examples presented in Figs. 1–4 also illustrate that the experimental asymmetric gating currents are not pure *m*-unit gating currents. In spite of the rather small magnitudes of the *n*- and *h*-unit gating currents they introduce an appreciable correction into the asymmetric gating current. Moreover, as the decay time of these currents is much larger they determine the whole of the tail end of the gating current.

The agreement between the experimental gating currents and those computed on the basis of the Hodgkin-Huxley equations supports the important assumption that the kinetics of the nerve membrane ionic currents are determined by the kinetics of structural transformations in the so-called gating units. On the other hand, one may view the above as supporting the interpretation that the experimentally measured asymmetric transient currents are actually the gating currents.

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