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Physicochemical model of Na^+ inactivation

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SUMMARY

A model of inactivation is proposed, based on the suggestion of transition from State Y with a high Na^+ conductance into the inactivated State Z without performance of work in the electric field. The theoretical steepness of the inactivation curve and the shift of this curve produced by changing the Ca^{2+} concentration contain one parameter. The value of this parameter has been estimated previously from the analysis of the activation processes. The theory agrees quantitatively with experimental results.

A qualitative explanation is given for the time course of inactivation and for the dependence of the time constant on the electric field and Ca^{2+} concentration.

A physicochemical scheme was proposed to describe the basic results of electrophysiological investigations dealing with the activation of ionic conductances in excitable membranes[1]. It was the purpose of this investigation to extend this scheme in order to examine the inactivation phenomena.

In order to explain the activation processes it was suggested that the membrane contains some activating sites (or particles) which can be transferred from State X, where they do not conduct Na^+, into State Y, corresponding to high Na^+ conductance. The transitions X $\rightleftarrows$ Y are coupled with a redistribution of the charge n. Per mole of particles the work $n\delta EF$ is performed in the electric field (E is the potential taken internally with respect to an external reference ground; F is the Faraday number; $\delta \leqslant 1$). At State X the site can bound Ca^{2+}, forming the State XCa ≡ S. Let us suggest further that the transition from State Y into an inactivated State Z can occur without any work of the charge. Then the transition into the initial State S requires work against the field forces equal to $-n\delta EF$. The corresponding set of reactions can be represented as in Fig. 1. Probably these transitions are connected with ion-exchange reactions and conformational transitions of the membrane macromolecules.

The equilibrium constants can be introduced as $K_i = k_i'/k_i$. According to the model, K_1 and K_3 do not depend on the field and

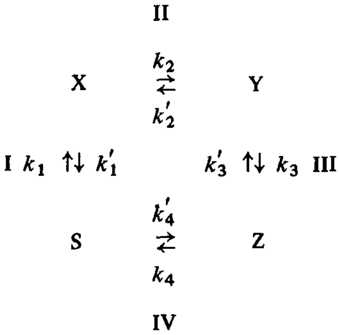

Fig. 1. Physicochemical scheme describing Na^+ conductance change. I, II, III, IV are the numbers of the reactions; k_i and k_i' (i = 1, 2, 3, 4) are the rate constants.

$$K_2 = q_2 \exp(-n\delta EF/RT) \tag{1}$$

where q_2 is constant. Let x, y, z and s be the fractions of the activating sites in States X, Y, Z and S, respectively; then

$$x + y + z + s = 1 \tag{2}$$

According to the described model[1] the Na^+ conductance is proportional to y:

$$g_{Na} = ky \tag{3}$$

Experiments show that the activation process occurs much more rapidly than the inactivation process. This permits a simplification of the analytical problem by assuming that States S, X and Y pass into equilibrium much more quickly than the system as a whole. When the depolarising step potential is applied to the membrane at first y increases, s and x decrease, but z remains practically unchanged ($z \simeq z_0$). The maximum value of y corresponding to the peak Na^+ current is nearly equal to the "quasi-equilibrium" value:

$$y^* = (1 - z_0)(1 + K_2 + cK_1K_2)^{-1} \tag{4}$$

where c is the concentration of Ca^{2+} in the surrounding solution.

If before the test potential step the membrane was held long enough at the conditioning prepotential E_0, the equilibrium between X, Y, Z and S was established. The initial value z_0 in these conditions is equal to the equilibrium value, z_e:

$$z_e = (1 + K_3 + K_{20}K_3 + cK_1K_{20}K_3)^{-1} \tag{5}$$

The index 0 is assigned to the parameters dependent on the prepotential E_0. Let us assume that the equilibrium of Y and Z is shifted towards Z, *i.e.* $K_3 \ll 1$. Putting Eqn. 5 into Eqn. 4 we get y^* as a function of the conditioning potential E_0. The dimensionless quantity h_∞, equal to the ratio of the peak Na^+ current to its maximal value at increasing conditioning hyperpolarization, was introduced by Hodgkin and Huxley[2]. Combining Eqns. 1, 4 and 5 we get:

$$h_\infty \equiv y^* / \lim_{E_0 \to -\infty} y^* = [1 + (1 + cK_1)^{-1} K_3^{-1} q_2^{-1} \exp(n\delta E_0F/RT)]^{-1} \tag{6}$$

The empirical function $h_\infty(E_0)$ obtained in ref. 2 is given by

$$h_\infty = [1 + \exp(-E_{0h}/7) \cdot \exp(E_0/7)]^{-1} \tag{7}$$

where E_{0h} is the empirical value of E_0 corresponding to $h_\infty = 0.5$ (E_0 and E_{0h} are measured in mV). It can be seen from Eqn. 6, that the steepness of the curve $h_\infty(E_0)$ is determined by the parameter $n\delta$ which enters the equilibrium constant K_2. It is clear from Fig. 1 that the same constant determines the activation process $X \rightleftarrows Y$.

Studying the activation process[1] we estimated the theoretical parameter $n\delta$ to be approx. 3.5. As $RT/F \simeq 25$ mV, the factor at E_0 determining the steepness of the curve $h_\infty(E_0)$ in the theoretical formula (Eqn. 6) is equal to 1/7 and agrees with the experimental value. Analysis of the pre-exponential factor in Eqn. 6 shows that, at the Ca^{2+} concentrations corresponding to $cK_1 \gg 1$, the *e*-fold increase of *c* produces a shift of the curve $h_\infty(E_0)$ along the E_0 axis of approximately 7 mV. Just such a shift was observed in ref. 3.

If the duration, t_0, of a conditioning prepotential step is not sufficient for the establishment of equilibrium, then in Eqn. 4 $z_0 \neq z_e$ and depends on t_0. In the adiabatic approximation, the inactivation kinetics are determined by Reactions III and IV. The function $z_0(t_0)$ can be obtained from the solution of the equation:

$$\dot{z}_0 = -(k_3' + k_{40})(z_0 - z_e)(1 - z_e)^{-1} \tag{8}$$

The solution has the form:

$$z_0 = z_e - (z_e - z_r)\exp[-(k_3' + k_{40})(1 - z_e)^{-1} t_0] \tag{9}$$

where z_r is the value of z corresponding to the initial resting potential, E_r. Putting Eqn. 9 into Eqn. 4 we get an exponential increase of the peak Na^+ current, I_{Na}, with t_0 if $z_0 < z_r$ (*i.e.* if $E_0 < E_r$), and a decrease of I_{Na} if $z_0 > z_r$ (*i.e.* $E_0 > E_r$). The time constant is equal to

$$\tau_h = (1 - z_e)(k_3' + k_{40})^{-1} \tag{10}$$

According to the theory of the absolute rates the constant k_{40} is proportional to $\exp(-n\delta E_0 F/2RT)$; k_3' must be proportional to *c* for $S \equiv XCa$. Taking into account Eqns. 1 and 5, we can see that the τ_h *vs.* E_0 relation is bell-shaped and that an increase in *c* shifts the "bell" to higher values of E_0 as was observed in ref. 3.

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