LETTER TO THE EDITOR

[Brief letters to the Editor that make specific scientific reference to papers published previously in THE JOURNAL OF GENERAL PHYSIOLOGY are invited. Receipt of such letters will be acknowledged, and those containing pertinent scientific comments and scientific criticisms will be published.]

Pronase and Models for the Sodium Conductance

Dear Sir:

Recently, Armstrong et al. (1973) have reported on the effects of internal perfusion of squid giant axons with the enzyme preparation Pronase. Elegant arguments were developed on the issue of the separate nature of the sodium and potassium conductances. I wish to comment here on the interpretation of another finding presented by these authors, that of a possible separation between the activation and inactivation processes of the sodium conductance ($g_{Na}$).

Armstrong et al. (1973) found that after internal perfusion with Pronase, the sodium currents were greatly prolonged, showing in fact no indication of a time-dependent inactivation. They suggested that their results could be accounted for if Pronase abolished inactivation, and in addition reduced $g_{Na}$, the maximum possible sodium conductance. Computations made, using Hodgkin-Huxley parameters, showed that this is indeed the case. By making $\tau_h$ (the time constant of inactivation) very long, and reducing $g_{Na}$ by a factor of about 3, it was possible to produce a good simulation of their Fig. 3 d.

The central question of interest, however, is not how to account for the effects of Pronase within the framework of Hodgkin-Huxley kinetics, but rather whether they do in fact bear on the issue of coupled vs. independent activation-inactivation kinetics. This point is illustrated by Fig. 1 b, which is also an excellent simulation of Fig. 3 d of Armstrong et al. (1973). Part 1 of Fig. 1 a and b has been computed from

$$g_{Na} = g_{Na}^0 \nu^5, \quad (1)$$

where $\nu$ is defined by the general second-order differential equation

$$\frac{d}{dv} (a + b) \dot{\nu} + ab(\nu - \nu_0) = 0, \quad (2)$$

with $a$, $b$, and $\nu_0$ functions of membrane potential only. Eqs. 1 and 2 constitute one example of a coupled activation-inactivation model, and have been used to describe the experimental behavior of the $g_{Na}$ in Myxicola axons (Goldman, 1974).

For a step in potential at time equals zero we may obtain a solution of 2.

$$\nu = \nu_0 - \left[ \frac{\dot{\nu}(0) + b(\nu(0) - \nu_0)}{a - b} \right] e^{-at} + \left[ \frac{\dot{\nu}(0) + a(\nu(0) - \nu_0)}{a - b} \right] e^{-bt}, \quad (3)$$

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FIGURE 1. Computed time-course of the sodium current under voltage clamp. Potential during the test step is 17 mV and the holding potential is -110 mV. Part 1 is computed from Eqs. 1 and 3 in the text with \( a = 5.8 \text{ ms}^{-1}, \beta = 0.3 \text{ ms}^{-1}, v(0) = 5.38 \text{ ms}^{-1}, \nu_e = 0.35, \nu(0) = 0.0, \) and \( g_{Na'} = 45 \text{ mmho/cm}^2 \). Part 2 is computed as in part 1 but with \( \beta = 0 \). In Fig. 1 b, part 1 is as in 1 a, part 1, and part 2 is as in 1 a, part 2, but with \( g_{Na'} = 21 \text{ mmho/cm}^2 \). Scale: 0.25 mA/cm\(^2\), 1 ms.

where \( v(0) \) is the initial value of \( v \), \( \dot{v}(0) \) is the initial velocity, and \( t = \text{time} \). Fig. 1 a, part 2, has been computed from Eq. 3 with \( \beta = 0 \), and Fig. 1 b, part 2 is as in Fig. 1 a, part 2, but with \( g_{Na'} \) reduced by about one-half.

Fig. 1 b indicates that separability of the activation and inactivation processes does not imply independence. This result could have been anticipated, as one view of the sodium gate consistent with Eqs. 1 and 2 is to imagine it to be composed of a number of independent subunits, each of the type:

- open
- resting
- inactivated.

This scheme provides more than one site for enzyme action to no less a degree than the \( m \) and \( h \) kinetics of Hodgkin and Huxley (1952).

Another way to express these results is to note that under quite general conditions a second-order variable can be transformed into a pair of independent first-order variables (see e.g. FitzHugh, 1969). One would not expect therefore that any given pharmacological treatment could ever be used to distinguish between coupled and independent models for \( g_{Na'} \).

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L. Goldman
Department of Physiology
University of Maryland
School of Medicine
Baltimore, Maryland 21201

BIBLIOGRAPHY


