## LETTER TO THE EDITOR

On Making Models of the Sodium Inactivation of Axonal Membranes

Dear Sir:

In a recent issue of the *Biophysical Journal*, data showing a shift with the test potential of the sodium inactivation curves in the squid axon (Hoyt and Adelman, 1970) were compared with a previously developed mathematical model (Hoyt, 1963; Hoyt, 1968). We wish to make two comments concerning the above papers: (*a*) that the existence of a pronounced shift in the inactivation depends on how the data are interpreted, and (*b*) that recent work by us (Moore and Jakobsson, 1970. Unpublished.) suggests that the cause of the inactivation shift in the Hoyt mathematical model is not its coupled nature but some other feature.

With regard to (*a*) above, the inactivation shift was seen by Hoyt and Adelman in the peak current ratios corrected for leakage. The existence of a pronounced shift in the data would seem to depend strongly on the magnitude of this leakage correction. The assumption underlying the leakage subtraction is that the resting sodium conductance through the time varying channel is essentially zero, and the resting membrane's permeability to sodium and other ions is accounted for by a separate "leakage channel." Since the peak transient currents are relatively small for low depolarizations, the leakage correction is proportionately more significant for small than for large cathodal step polarizations. It is therefore critical to use the correct leakage value which is itself determined in part by the basic assumption of whether or not sodium current through the specific permeability channel contributes to the leakage conductance.

With regard to (*b*) above, we have recently investigated the properties of the following model, which appears to fit Hoyt's definition of being "coupled":

$$S_c \xrightleftharpoons[k_{-r}[Ca]_o]{k_r} S_r \xrightleftharpoons[k_{-m}[Ca]_o]{k_m} S_m \xrightleftharpoons[k_{-h}]{k_h} S_h, \tag{1}$$
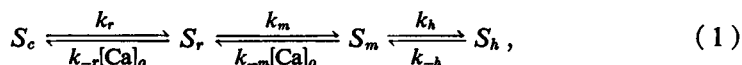
where S_r and S_c are, respectively, singly and doubly bound with calcium ions, k_{-m} and k_{-r} are calcium binding rates, k_h and k_{-h} are rates of conformational change. The term S_m is related directly to the sodium permeability. If k_r and k_{-r} are assumed rapid relative to the other rate constants, equation 1 goes into a form suggested by Hoyt (1970):

$$R \rightleftharpoons A \rightleftharpoons B, \tag{2}$$

where the sodium conductance i a function of [*A*]. Equation 2 does not lead to the Hoyt equations (Hoyt, 1968), but to a different coupled model. We have found that the model represented by equation 2 for values of the parameters which in general give a good fit to the axon data, shows no significant shift in the inactivation curve as the test pulse magnitude is varied. The inactivation is given essentially by the expression $1 - [B]$ (or $1 - [S_h]$ in the terminology of equation 1). Since our coupled model does not demonstrate the inactivation shift, we believe that the feature of the Hoyt model which causes the shift is not its coupled behavior, but rather something else.

Concerning the issue of what might cause the inactivation shift, we note that a fundamental difference between our model and the Hoyt model is that our model leads to a set of first-order differential equations in which the time derivative of each system variable is coupled to the values of both variables; that is, $\dot{S}_m$ and $\dot{S}_h$ are each a function of both S_m and S_h. On the other hand, in the Hoyt model the coupling is in one direction only, where $\dot{\nu}$ is a function of both ω and ν, but $\dot{\omega}$ is a function of ω only. We thus offer as a speculation that it may be this specifically unidirectional nature of the Hoyt coupling which causes the shift.

We hope that this note will contribute to a further clarification of the very interesting issues which Hoyt and Adelman have raised concerning the behavior of the sodium system and how it may be modeled.

REFERENCES

HOYT, R. 1963. *Biophys. J.* 3:399.
HOYT, R. 1968. *Biophys. J.* 8:1074.
HOYT, R. 1970. *Biophys. Soc. Annu. Meet. Abstr.* 10:184A.
HOYT, R., and W. ADELMAN. 1970. *Biophys. J.* 10:610.

E. JAKOBSSON
L. E. MOORE
Department of Physiology
Case Western Reserve University
School of Medicine
2109 Adelbert Road
Cleveland, Ohio 44106