To the Editor: In the June 2004 issue of the Journal of Neurophysiology, in their paper “Analysis of the Optimal Channel Density of the Squid Giant Axon Using a Reparameterized Hodgkin–Huxley Model,” Sangrey and coworkers model the gating current using the voltage-capacitance measurements of Fernandez et al. (1982). There are several problems with their approach.

1) Sangrey and colleagues interpret the experimental results of Fernandez et al. (1982) as evidence that for the squid giant axon the maximum change of the voltage-dependent part of the capacitance occurs at the resting potential. Actually it is not possible to draw such a conclusion from these experiments. The measurements by Fernandez et al. were done at varying holding potentials in the frequency domain. Previous work by Bezanilla et al. (1982) measured \( Q_g \) versus \( V_m \) curves, which exhibit a rather unexpected behavior. The curves shift depending on the holding potential at which the measurements are done. For this reason the frequency domain measurements at different holding potentials do not translate in any transparent way into a voltage dependency of the gating capacitance during the propagated action potential. A more relevant description of the gating capacitance during the propagation was published by Armstrong and Bezanilla (1975). They measured the differential capacitance of an axon at 10-mV pulse intervals starting from a holding potential of \(-70 \text{ mV}\). This time course is more like the time course of an action potential than the measurements done at different holding potentials. Figure 9 of their work shows that the gating capacitance increases from \(-70 \text{ mV}\), reaches a maximum of 0.35 \( \mu \text{F/cm}^2 \) at \(-10 \text{ mV}\), and then decreases. The assumption that the gating capacitance starts at a maximum at the resting potential and then decreases as \( m(t) \)—the fraction of gating particles traversing the membrane—increases is incorrect.

2) Equation 3a of Sangrey et al. (2004) \[ Q_g(t) = C_g(t)V_m(t) \] implies that \( C_g(t) = Q_g(t)/V_m(t) \). However, the gating capacitance is voltage dependent and for the steady propagation of the action potential it can be described as an instantaneous function of the potential alone. A general definition of capacitance, which includes a nonlinear relation between \( Q \) and \( V \), is the differential capacitance given by

\[
C = \frac{dQ}{dV}
\]

Notice that when \( Q \) is a linear function of \( V \), the above definition reduces to the well-known expression for capacitance of \( C = Q/V \).

The correct, model-independent expression for the gating current \( I_g(t) \) during propagation is

\[
I_g(t) = \frac{dQ}{dt} \frac{V_m}{dV_m} = \frac{dQ}{dt} \frac{dV_m}{dV_m} dt
\]

and using the definition of differential capacitance introduced above we get

\[
I_g(t) = C_g(V_m) \frac{dV_m}{dt}
\]

To estimate the velocity dependency on gating capacitance Hodgkin (1975) simply assumed that the charge transfer as a function of the potential is linear; in other words gating capacitance is a constant. Adrian (1975) assumed that the time evolution of the gating charge during propagation was given by

\[
Q_g(t) = Q_{g,\text{max}} m(t)
\]

where \( m \) represents the fraction of \( m \)-particles in the position giving rise to open sodium channels and \( Q_{g,\text{max}} \) is the maximum transferred charge. Assumption 2 is supported by a similar time evolution of \( Q_g(t) \) and \( m(t) \), both saturating at the foot and the peak of the action potential with fastest growth in between. The gating current is then

\[
I_g(t) = Q_{g,\text{max}} \frac{dm}{dt} = Q_{g,\text{max}} \frac{dm(V_m)}{dV_m} \frac{dV_m}{dt} = C_g \frac{dV_m}{dt}
\]

It turns out that numerical calculations using the \( \text{H}–\text{H} \) equations show that for the rising phase of the propagated action potential \( m(V_m) \) is approximately proportional to \( V_m \) (see, e.g., Fig. 1 of Hunter et al. 1975). Therefore

\[
C_g = Q_{g,\text{max}} \frac{dm}{dV_m}
\]

becomes a constant during the rising phase of the action potential. Thus the net result is that Adrian’s gating current addition (Eq. 3) is approximately equivalent to increasing the capacitance of the membrane by a constant value independent of further modeling. The conclusion is that the gating charge of the sodium channel increases the membrane capacitance and affects the conduction velocity as Hodgkin correctly indicated in 1975.

REFERENCES


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