LETTER TO THE EDITOR

Is the Delayed Rectifier the Major Pathway for Resting K Current?

Dear Sir:

The comments by John Clay (1988) on my paper (Chang, 1986) are very interesting. The control mechanism of the resting potential is a fundamentally important issue in electrophysiology that has not been thoroughly investigated. Therefore, I think the suggestions made by Clay deserve careful consideration.

The basic question here is whether the major pathway of the resting current is controlled by the excitable K channel (i.e., the "delayed rectifier") or not. Clay suggested that by combining the Goldman-Hodgkin-Katz (GHK) equation with the Hodgkin-Huxley model (Hodgkin and Huxley, 1952), it is possible to explain my data (Chang, 1986) based on the properties of the delayed rectifier. However, there seem to be some difficulties with this approach. First, let us examine this approach from a theoretical point of view. What Clay essential did was assume that the premeability ratio P_K/P_{Na} in the GHK equation has a specific voltage dependence such that $P_K(V) \rightarrow n_\infty^4$ and $P_{Na} \rightarrow$ constant, where n_∞^4 is the V dependence of the delayed rectifier as described by Hodgkin and Huxley (1952). Such an approach involves some conceptual problems. For example, the I-V relationship given by the GHK equation is different from the Ohm's law assumed by the Hodgkin-Huxley model. The electrodiffusion model of GHK is a special solution of the Nernst-Planck equation which described macroscopic transport phenomenon. It is not supposed to apply to narrow pores as envisioned by the Hodgkin-Huxley model (Hodgkin and Keynes, 1955). Although I agree that the Ohm's law assumed by the Hodgkin-Huxley model is an oversimplification, I still think one needs to be aware of the problem of conceptual consistency in mixing the GHK equation with the Hodgkin-Huxley model.

Next, let us examine the issue from an experimental point of view. It appears that there are several problems with Clay's model: (*a*) The value of the background conductance chosen by Clay ($g_{bg} = 2.2\ \mu S/cm^{-2}$) is far too small. We have measured the resting conductance of squid axon under the conditions that the Na channel was blocked by tetrodotoxin and the delayed rectifier was blocked by 4-aminopyridine. The average resting conductance (from five axons) was 0.36 ± 0.14 mS/cm^2. This value is consistent with the findings from other laboratories since the resting membrane conductance of a large unmyelinated axon is known to be 0.2–1.0 mS/cm^2 (Hille, 1984). Thus the value of g_{bg} chosen by Clay is almost two orders of magnitude smaller than the typical experimental value. Clay's argument that the g_{bg} deduced from in vivo recording might be very low is irrelevant because the data reported in my study (Chang, 1986) were obtained from in vitro preparations, not in vivo preparations. (*b*) Clay's model predicts a very steep voltage dependence of I_K. According to his Eq. 2, I_K at $V = -60$ and -70 mV is 0.31 and 0.025 μA/cm^2, respectively. Thus, his model predicts a 12-fold increase of I_K when V is changed from -70 to -60 mV. However, results of our V-clamp measurements indicate that the membrane conductance does not change very steeply with potential at the resting state. Also, we recently measured the ^{42}K efflux across the squid axon membrane as a function of potential (Hunt and Chang, 1987). It was observed that the ^{42}K efflux varied only slightly (< 1.5-fold) between -60 and -70 mV. This lack of a steep V dependence implies that the major pathway for the resting current is not the excitable K channel. (*c*) Even if one accepts Clay's model, the I_K through the K channel is still too small to account for the resting current. According to the n_∞^4 function, the conductance through the K channel at $V = -70$ mV is 0.039 mS/cm^2. The resting conductance of the squid axon at -70 mV as determined from voltage-clamp measurements is typically 0.8 mS/cm^2. Therefore, the conductance contributed by the delayed rectifier can only account for 5% of the total resting conductance. It is apparent that the delayed rectifier is not the major pathway of the resting current.

I do agree with Clay on one point, which is that the TEA blockage of the K channel may vary with the membrane potential. We estimated that at $V = -60$ mV, 20 mM TEA can block at least 75% of the excitable K conductance. It is difficult to determine precisely the TEA blockage near the resting potential because the excitable K current is small in comparison with the total resting current. Because we were aware of this difficulty, we also used 4-aminopyridine and K-free treatments to block the delayed rectifier.

In summary, although Clay's model is able to provide a good fit to my data, I suspect that such fitting is fortuitous because the background conductance (i.e., g_{bg}) chosen in his model was unusually small. Recently, we have extended our work to study the effects of various cations on the membrane potential, membrane conductance, and isotope-labeled efflux in the resting axon. We found that the control mechanism of the resting conductance is very complicated. The semipermeable property of the resting membrane appears to be controlled by more than one type of K channel. The major type of resting K channel has a slight tendency of inward rectification and is activated at a voltage below the normal resting potential (Chang, 1987). It has an ion-selectivity sequence similar to that of the resting membrane, and its pharmacological properties differ from those of the delayed rectifier K channel (Chang et al., 1987). Most recently, we discovered evidence of a Mg-activated inward rectifying K channel that is present only in the intact axon but not in the perfused axon (Chang and Hunt, 1988). We suspect that this channel may also contribute to part of the resting conductance. Apparently, a large amount of work is required before we can fully understand what really controls the membrane pathways of the resting currents.

Notes added in proof: (1) Recently Haydon et al (*J. Physiol.* 402:363–374, 1988) reported that the "leakage conductance" of the squid axon is 0.3 mS/cm^2, which is in good agreement with my estimate of g_{bg}. These authors also concluded that a major component of the K conductance of the resting axon is different than the Hodgkin-Huxley delayed rectifier. (2) The resting potential quoted by Clay (-67.2 ± 2.9 mV) was obtained under the condition $K_o = 0$, not $K_o = 10$ mM.

Received for publication 15 March 1988 and in final form 11 July 1988.

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