BRIEF COMMUNICATION

THE STANDARD HODGKIN-HUXLEY MODEL AND SQUID AXONS IN REDUCED EXTERNAL Ca^{++} FAIL TO ACCOMMODATE TO SLOWLY RISING CURRENTS

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ABSTRACT Accommodation may be defined as an increase in the threshold of an excitable membrane when the membrane is subjected to a sustained subthreshold depolarizing stimulus. Some excitable membranes show accommodation in response to currents which rise linearly at a very slow rate. In this report we point out a theoretical and an experimental counterexample, i.e., a nerve model and an axon which do not accommodate. The nerve model is the standard Hodgkin-Huxley axon, which Hodgkin and Huxley expected not to be excited by a very slowly rising current. This expectation is often quoted as fact, in spite of contrary calculations which we confirm. We have found that squid axons in seawater with reduced divalent cation concentration also do not accommodate to slowly rising currents.

In 1952, the British physiologists A. L. Hodgkin and A. F. Huxley published their pioneering work that culminated in the construction of a quantitative model for the generation of the action potential in squid giant axons. They were subsequently rightly honored with the Nobel Prize in Physiology, since their efforts laid the conceptual foundations for virtually all later progress in electrophysiology. However, one passage in the discussion of the fourth and last paper of their classic series may have engendered a misconception, which has persisted to this day, about the behavior of the Hodgkin-Huxley model. The passage in question is (Hodgkin and Huxley, 1952):

> *Accommodation.* No measurements of accommodation were made nor did we make any corresponding calculations for our model. It is clear, however, that the model will show "accommodation" in appropriate cases. This may be shown in two ways. First, during the passage of a constant cathodal current through the membrane, the potassium conductance and the degree of inactivation will rise, both factors raising the threshold. Secondly, the steady state ionic current at all strengths of depolarization is outward (Figure 11), so that an applied cathodal current which rises sufficiently slowly will never evoke a regenerative response from the membrane, and excitation will not occur.

The implication in this passage seems to be that both actual excitable membranes and also the Hodgkin-Huxley model will accommodate to a very slowly rising current without producing

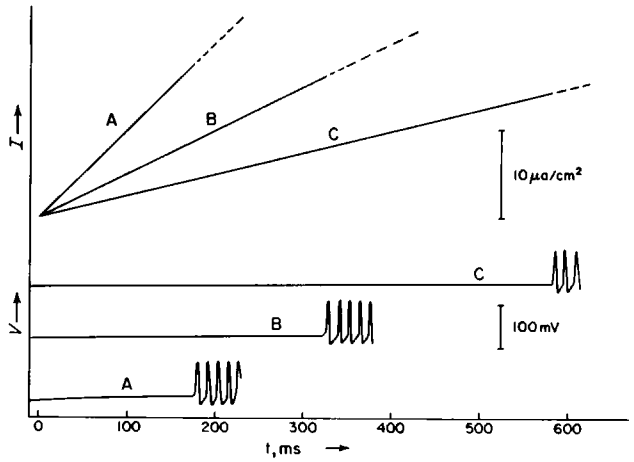

FIGURE 1 Response of space-clamped Hodgkin-Huxley axon with standard parameters (Palti, 1971) to linearly rising current. Integration method is the stiff differential equation solver of Gear, used with the IBM CSMP-3 package (Speckhart and Green, 1976). Slope with which current is applied, in $\mu A/cm^2$-s, is: *A*, 10; *B*, 5; *C*, 2.5. Transition from solid to dashed lines on current representation occurs at onset of action potential train.

action potentials. However, the first computer simulations of the Hodgkin-Huxley model revealed no minimal slope of current (Cole et al., 1955; FitzHugh and Antosiewicz, 1959) although of course this observation does not prove there is none, since for any slope tried a smaller one could be hypothesized. Subsequently there has been achieved sure knowledge that the H-H model with standard parameters has no minimal slope, by virtue of stability analysis of singular points on the model's steady state current-voltage curve (Chandler et al., 1962; Cooley et al., 1965; FitzHugh, 1969). This analysis shows that there is a region on the I–V curve where the singular points are unstable. The inference to be drawn is that when the current is turned on so that the unstable region is entered, the system will begin to oscillate and produce action potentials no matter how slow the current turn-on.

Unfortunately some of the above-cited literature is not as well known as it should be, since present-day works continue to state that the Hodgkin-Huxley model accommodates to slowly rising currents without firing action potentials (Orkand, 1977; Scott, 1977). An explicit computer simulation of the Hodgkin-Huxley model producing action potentials in response to very slowly rising currents is shown in Fig. 1.

In contrast to the Hodgkin-Huxley model, actual space-clamped excitable membranes have up to now been seen to accommodate to slowly rising currents (Vallbo, 1964 *a* and *b;* Hagiwara and Oomura, 1958; Katz, 1966). It has also been found that the Hodgkin-Huxley model and the corresponding Frankenhaeuser-Huxley model for amphibian node can be made to accommodate by changing some of the voltage-dependent parameters (Frankenhaeuser and Vallbo, 1965).[1] The same changes which make the model accommodate also suppress repetitive firing in response to constant current stimuli (Khodorov, 1974). This connection

[1]Several workers, including one of the authors (E. Jakobsson) have done such computations for the Hodgkin-Huxley squid model, but they have not been published.

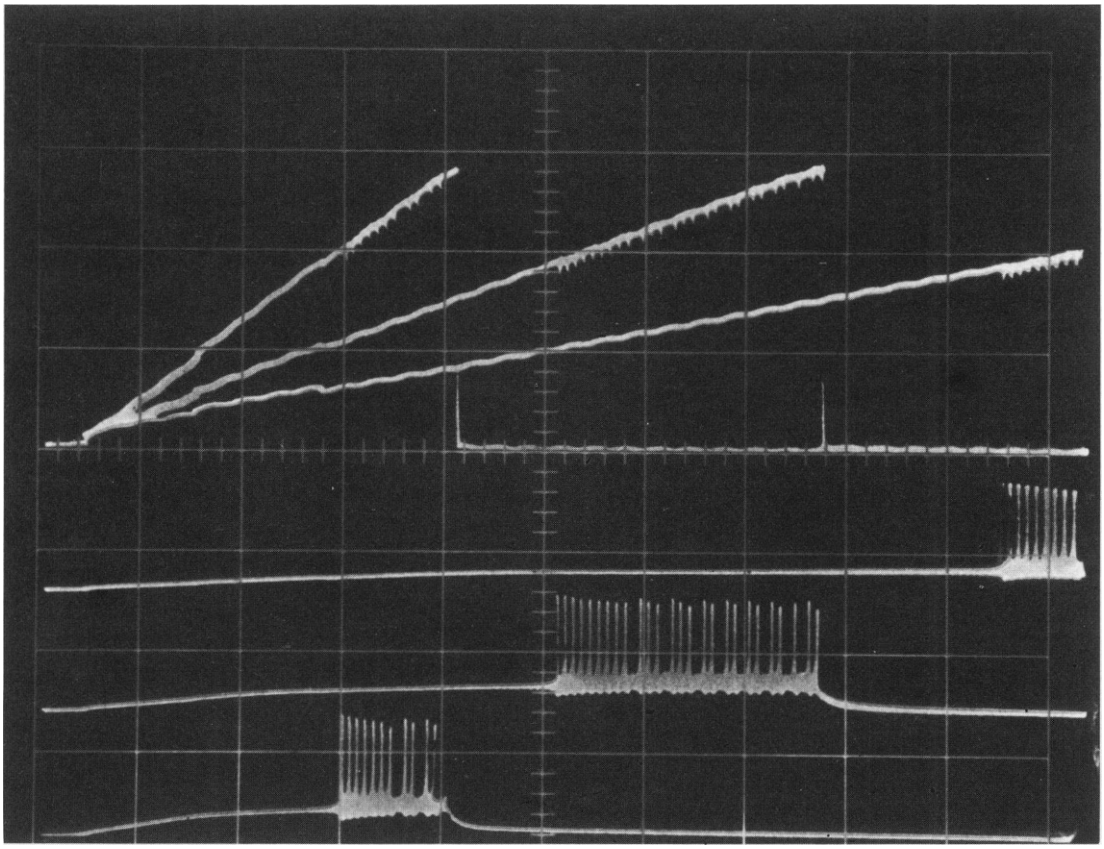

FIGURE 2 Slowly rising current applied to squid axon. Upper traces are current, lower traces are voltage. Scales are 100 mV/div, 0.5 μA/div, 50 ms/div. Since membrane surface area is estimated to be 0.01 cm^2, current slopes are 100, 200, and 400 μa/cm^2-s. Modified artificial seawater with 0 Mg^{++}, 10 mM/liter Ca^{++}. Temp, 22.3°C. Double sucrose gap. For further details of experimental method see Guttman and Barnhill, 1970.

between accommodation and repetitive firing in nerve models led us to ask the following question of some actual squid axons: If particular changes in the model parameters both suppress repetitive firing and induce accommodation, would changes in the axon bathing solution which induce repetitive firing also eliminate accommodation? We can often make squid axons fire repetitively by reducing extracellular divalent cations.[2] Would this change eliminate accommodation?

Fig. 2 shows a result typical of those we obtained for slow ramp current stimulation in low divalent cation concentration, for squid axons in which an excitable patch of membrane was isolated by a double sucrose gap. For squid axons in our double sucrose gap apparatus in normal $[Ca]_o$, liminal slopes at this temperature were generally $>10^4$ μA/cm^2-s (Guttman, 1968). Thus the maximum current slope in Fig. 2 (200 μa/cm^2-s) is about two orders of

[2]Repetitive firing of nerve when divalent cations are reduced is quite an old finding. Among the early reports are Katz, 1936; Arvanitaki, 1939; Brink et al., 1946.

magnitude less than the liminal slope under ordinary circumstances. Note that there is no trace of accommodation. Rather the nerve begins to fire action potentials at a similar value of current for each depolarization, no matter how slowly the current was turned on. In fact, there is a slight but possibly significant reverse accommodation; for more slowly rising stimuli, the value of current at the beginning of the action potential train is slightly lower than for more rapidly rising stimuli. The Hodgkin-Huxley model clearly shows "reverse accommodation." In the simulations of Fig. 1, the values of current at the onset of the *a. p.* trains for curves *A, B,* and *C* were 18.1, 16.5, and 14.4 $\mu A/cm^2$, respectively. All in all, Fig. 2 looks remarkably like Fig. 1. However, it must be emphasized that this does not necessarily mean that the computer model used to generate Fig. 1 depicts in detail the processes in the axon which resulted in the responses of Fig. 2. In fact, we know of several factors likely to influence the response of the squid axon in Fig. 2 which are simply not included in the computer model of Fig. 1, including K^+ accumulation in the periaxonal space (Frankenhaeuser and Hodgkin, 1956; Adelman and FitzHugh, 1975), those features of Na^+ inactivation which are not described by the Hodgkin-Huxley model (for a review of such features, see Jakobsson, 1978 *a* and *b*), the alteration of voltage-dependent parameters by changes in divalent cation concentrations (Frankenhaeuser and Hodgkin, 1957; Shoukimas, 1978), and the hyperpolarizing current induced by the sucrose gap (Julian et al., 1962). The similarities between Figs. 1 and 2 imply only that the system topologies are similar, in terms of the existence and stability of limit cycles and singular points. (For a review of the topology of the H-H equations, see Rinzel, 1978. For new results on squid axon phase space topology, see Guttman et al., 1980.) Quantitative differences between the systems of Figs. 1 and 2 are suggested by the much larger current densities of Fig. 2. This is partly because the membrane leak conductance is higher in low Ca^{++} and partly because of the stimulating current required to overcome the sucrose gap hyperpolarizing current mentioned above. In constructing the system's equivalent circuit, the sucrose gap current may reasonably be represented by an increase in magnitude of the leak conductance and a hyperpolarizing shift in its reversal potential. Thus the same experiment in an axial wire arrangement would be expected to yield somewhat different results. It seems to us that as long as one understands the difference between the sucrose gapped and the axially wired preparations, either is appropriate for accommodation experiments in low Ca^{++}. In both cases the axon membrane, under the influence of an unphysiological bathing solution, is performing a function it never performs in vivo. We are using the axonal membrane as a model system to try to understand what might normally happen at axon hillocks or receptor endings, where time-varying stimulation is transduced into trains of action potentials. There is no *a priori* way to know whether the sucrose gapped or the axially wired preparation is the better model for such events.

We conclude that accommodation to very slowly rising currents is not a universal feature of either actual nerve membranes or realistic nerve membrane models. Either entity may or may not accommodate, depending on the values of the voltage-dependent rate constants for the processes underlying excitability.

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