A Single Channel or a Dual Channel Mechanism for Nerve Excitation

Dear Sir:

Narahashi and Haas (1968) and Hille (1968) have suggested that data obtained when various pharmacological agents are applied to nerve make it likely that the channels in the axon membrane that carry Na and K are separate entities in contrast with the suggestion that there is a single channel (Mullins, 1959) that modifies its selectivity first in favor of Na and later in favor of K. My purpose is to examine the assumptions underlying the analysis that has been made and to show that the evidence for two channels is not at present compelling.

The models to be considered are shown below.

**Single Channel Scheme**

Impermeable (A) $\xrightarrow{m}$ Na Permeable $\xrightarrow{h}$ Impermeable (B) $\xrightarrow{n}$ K Permeable

**Separate Channel Scheme**

Na Channel Impermeable $\xrightarrow{m}$ Na Permeable

K Channel Impermeable $\xrightarrow{n}$ K Permeable

Implicit in the single channel scheme is the assumption of a single, voltage-dependent, time constant that controls the change of the membrane from Impermeable (A) to K Permeable. The Na Permeable phase is governed by two subsidiary time constants and any appreciable lengthening of especially the $h$ process will preclude the appearance of the K Permeable state. The two-channel scheme has a Na Permeable state that can be turned on by the $m$ process and turned off either by promoting $h$ or by a voltage change reversing $m$, while the K process, independent of the Na channel, is turned on or off by the $n$ process. For either scheme it is necessary to suppose that the membrane has a dispersion of channel time constants so that there is some overlap between Na and K currents flowing through the membrane.

The classical Hodgkin-Huxley analysis treated the three processes, represented by the conductance variables $m$, $h$, and $n$ as independent of each other, but the analysis
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itself does not imply either a single channel or a dual channel mechanism, concerned as it is only with convenience in representing the phenomena of excitation.

One may well ask what sort of experimental demonstration would be conclusive in showing that there were two channels in the excitable membrane. The maximum values of partial ionic conductance, \( g_{Na} \) and \( g_{K} \), are about the same for lobster and squid axons (Narahashi and Haas, 1968; Cole and Moore, 1960) and are each about 100 mmho/cm². If there were two channels, both could, in principle, be opened at the same time; the membrane conductance of the axon would then be 200 mmho/cm². There is not, however, any experimental data where the membrane conductance exceeds the maximum value of the conductance for a single ion, or, 100 mmho/cm². This is an important point because the fact that the conductance does not exceed a single ion conductance makes it possible in principle for a single channel to carry either \( Na \), \( K \), or a mixture of these ions.

A key observation in the two-channel argument is that tetrodotoxin (TTX) when applied to the outside of axons is able to block the \( Na \) current without influencing either the time course or the magnitude of the \( K \) current. The inference drawn from such an experiment is that TTX has blocked the \( Na \) channels and left the \( K \) channels unaffected. In the absence of specific information as to how \( g_{Na} \) is increased in response to depolarization, it is equally possible to suppose that TTX changes the channel size or channel affinity for \( Na \) without TTX entering the channel.¹ Such an arrangement could be brought about in a variety of ways that are not relevant to the present argument; it is perhaps simplest to distinguish between a channel assuming \( Na \) selective form and the ability of \( Na^+ \) to flow through the channel. The channel selectivity depends upon a membrane time constant controlling the opening and closing of the channel to \( Na \) and a final opening of the channel to \( K^+ \). Whether any ions flow through the channel could depend on the modulating influence of substances present at the channel entrance on either side of the membrane.

A second pharmacological argument used in favor of separate channels for \( Na \) and \( K \) is the effect of tetraethylammonium ion (TEA) in blocking \( K^+ \) currents while leaving unaffected the \( Na^+ \) currents of the axon (Hille, 1967; Armstrong and Binstock, 1965). This effect is related to that produced by introducing \( Cs^+ \) inside the axon, where \( I_K \) is blocked with an increase in the duration of \( I_{Na} \) (Adelman and Senft, 1966 a) and to the introduction of a high \( Na \), low \( K \) inside the axon where the sodium currents are greatly prolonged (Adelman and Senft, 1966 b). What all these observations suggest is that the internal ionic composition of the axon affects \( K \) and \( Na \) currents in a way that is not clearly understood but is most easily summarized by saying that foreign cations compete with \( K^+ \) for transfer so that the apparent number of \( K \) channels is greatly reduced. While the effect of TTX is poorly reversible, the effect of TEA is reversible so that it is possible to assume that this ion enters channels in the \( K \) form and so lowers channel mobility for \( K \) that no \( K \) current flows. It is,

¹The TTX molecule is rather large compared with what one imagines is a plausible value for channel size. The fact that TTX acts only when applied to the outside of the membrane favors the notion that it cannot pass through the membrane and may well act at a site distant from the \( Na \) channel.
of course, equally reasonable to assume that TEA acts at a site different from the K channel and merely prevents the channel from attaining the proper size or affinity so that it can carry K⁺.

A final pharmacological argument (Narahashi and Haas, 1968; Hille, 1968) concerns the effects of dichlordiphenyl-trichloroethane (DDT) on the Na and K currents in frog nodal membranes and in lobster axons. The effects of DDT on these two membranes are not identical but for the present discussion the differences are not important. The principal actions of DDT are: (a) about a 5-fold slowing in the rate at which the Na current is turned off by inactivation, and (b) about a 3-fold decrease in the maximum value of gK, the potassium conductance. There are, in addition, less important changes in the rate of turning on of INa and IK. The result of these changes induced by DDT is that a very appreciable Na⁺ current continues to flow at times as long as, for example, 5 msec following a depolarizing pulse while in a normal axon depolarized to 0 mv such a Na current would be entirely negligible. Since, at 5 msec IK has been turned on, the fact that Na and K currents flow at the same time has been used as evidence in support of a two-channel mechanism. What has been overlooked in this analysis is the very large effect that DDT has in reducing the maximum value of gK. As an example, at 5 msec, INa in a DDT-treated lobster axon has been inactivated to about half its initial value for a depolarization to −20 mv while IK is not quite at its steady-state value. The corresponding conductances for Na and K are gNa = 50 mmho/cm² and gK = 30 mmho/cm² so that the sum is 80 mmho/cm², a value appreciably less than that of the maximum peak² gNa which is 100 mmho/cm². It would appear, therefore, that the results obtained with DDT support, if anything, a single-channel model for nerve excitation in the sense that gK is appropriately reduced as the time course of gNa is prolonged.

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REFERENCES


I have used the maximum peak gNa because it is an experimentally measured quantity. The Hodgkin-Huxley gNa is about twice as great and implies that (on a single channel scheme) only half the Na channels reach a K-carrying state.
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