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Propagation of electrical signals along giant nerve fibres

By A. L. Hodgkin, F.R.S. and A. F. Huxley

In this part of the discussion we shall attempt to describe the way in which electrical signals are propagated along the giant nerve fibres of squids and cuttlefish. These fibres consist of cylinders of protoplasm, 0·2 to 0·6 mm in diameter, and are bounded by a thin membrane which acts as a barrier to ionic movement. The protoplasm, or axoplasm as it is commonly called, is an aqueous gel which is a reasonably good conductor of electricity. It contains a high concentration of K^+ and a low concentration of Na^+ and Cl^-, this situation being the reverse of that in the animal's blood or sea water. Axons which are left in sea water slowly lose potassium and gain sodium. This process takes about 24 hours and is roughly 30000 times slower than the diffusion of ions out of a cylinder of gelatin of the same size. The interchange of sodium and potassium is very greatly accelerated by stimulating the fibres. Experiments with tracers, such as those made by Keynes & Lewis (1951) or Rothenberg (1950), allow the interchange to be measured quantitatively, and there is general agreement that the impulse is associated with an entry of 3 to 4 $\mu\mu$mol of Na^+ through 1 cm^2 of membrane and an exit of a corresponding quantity of K^+. These quantities are very small compared with the total number of ions inside the fibre. In the giant axon of the squid the quantity of potassium lost in each impulse corresponds to only about 1 millionth of the total internal potassium. One would therefore expect that a giant fibre should be able to carry a great many impulses without recharging its batteries by metabolism. On the other hand, a very small fibre such as a dendrite in the central nervous system should be much more dependent on metabolism since the ratio of surface to volume may be nearly 1000 times greater.

The facts which we have outlined raise two important problems. First, how does a nerve fibre use the energy derived from the mixing of sodium and potassium ions to generate and conduct an electrical impulse? Secondly, how does it use the energy derived from metabolism to separate K and Na in the first instance or to restore the *status quo* after activity? Our experiments have been largely concerned with the first problem, and it is this aspect that will be discussed here.

In order to study the factors controlling ionic movements in the squid giant axon, we measured the current which flows through about 10 mm^2 of membrane when it is depolarized by a known amount. As an illustration we shall consider the flow of current when the membrane is depolarized by 65 mV (figure 5*a*). The first event is a brief surge of capacity current which occurs so rapidly that it is barely visible on the time scale employed. (Other records show that it corresponds to the sudden charging of a membrane capacity of 1 μF/cm^2.) This is followed by a phase of inward current which is transient and soon gives place to a maintained phase of outward current. The interesting thing about the phase of inward current is that it is in the opposite direction to that in a stable system. If it had not been drawn off by the feedback amplifier used to maintain the membrane at a constant potential, the inward current would have depolarized the membrane

at about the same rate as that observed during the rising phase of the action potential. According to the sodium hypothesis the active depolarization of a nerve fibre is due to entry of Na^+. The inward current seen in figure 5 should therefore disappear when external Na^+ ions are removed. As a substitute for Na^+ we followed Lorente de Nó (1947) and employed choline which seems to be totally inert in the squid giant axon. Figure 5*b* gives the effect of removing Na^+ and 5*c* shows that the action is reversible. It will be seen that the phase of inward current disappears when Na ions are removed and is replaced by a hump of outward current. The later stages of the record are little affected by removing Na^+. A simple explanation of this experiment is that the initial ionic current is due to

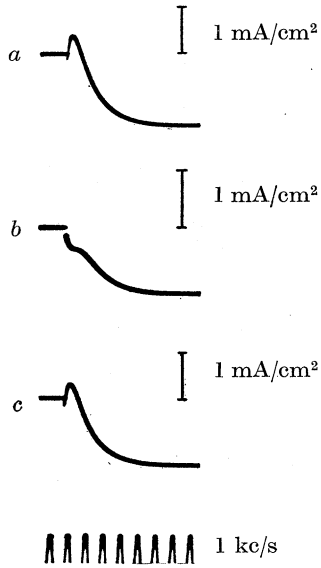

FIGURE 5. Records of membrane current associated with sudden reduction of membrane potential by 65 mV; temperature 11° C; inward current shown upward. *a*, axon in sea water. *b*, axon in Na-free choline sea water. *c*, after replacing sea water. (From Hodgkin & Huxley 1952*a*.)

an increase in permeability which allows Na^+ ions to move down their electrochemical gradient. In the case of record *b* there were no sodium ions in the external medium, and the initial ionic current is due to the outward movement of the internal sodium ions. In records *a* and *c* sodium ions were present in high concentration outside the fibre so that the inward movement predominates and therefore produces a net inward current.

Figure 6 illustrates a related phenomenon. In this experiment the nerve was kept in sea water throughout the experiment, but the degree of depolarization was varied. The initial ionic current is inward with depolarizations of 91 and 104 mV but is replaced by a hump of outward current with depolarizations of 130 and 143 mV. At 117 mV the initial phase has disappeared and the total current is small for a period of about 0·5 ms. We therefore take -117 mV as the equilibrium potential for the sodium ions. In this experiment the resting

potential was about 65 mV, so that the reversed potential difference which just balances the tendency of sodium ions to move inwards from the more concentrated external solution was 52 mV. This gives an internal sodium concentration of about 50 mM which agrees reasonably with chemical estimates. The method of measuring the sodium potential illustrated by figure 6 can be tested by varying the sodium concentration in the external fluid. It is found that the change in sodium potential varies with external Na^+ in the manner predicted by the Nernst equation for a sodium electrode. Thus a tenfold change in sodium concentration alters the critical potential by 55 mV at 8° C.

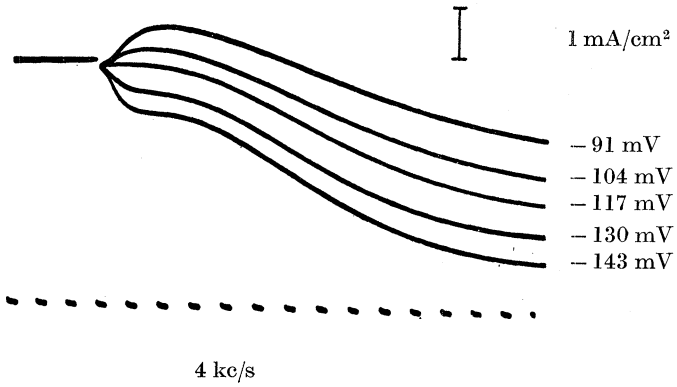

FIGURE 6. Records of membrane current associated with large depolarizations; temperature 3·5° C; inward current shown upwards; nerve in sea water. The numbers attached to the curves give the displacement of the membrane potential from its resting value. (From Hodgkin, Huxley & Katz 1952.)

The delayed outward current seen in figures 5 and 6 is little affected by changing the sodium concentration and is almost certainly not due to sodium movement. This current is of the right sign and magnitude to explain the repolarization of the membrane during the falling phase of the action potential. Since this process is thought to depend on an outward movement of potassium ions, it is possible that the prolonged current may be due to the movement of potassium ions down their electrochemical gradient. In order to test this point we compared the steady current associated with depolarization of a *Sepia* axon with the outward movement of potassium ions measured with ^{42}K. We found that the outward flux of potassium was reduced under an anode and was very greatly increased under a cathode. With steady cathodal currents there was good agreement between the total current measured electrically and that calculated from the movement of potassium ions on the assumption that these were the only ions concerned in carrying the current.

We have now obtained evidence that the early current in a depolarized axon is largely sodium current and the delayed current is largely potassium current. By making certain rather general assumptions it is possible to obtain the complete time course of these two components of the ionic current (Hodgkin & Huxley 1952*a*). The permeability of the membrane to the sodium and potassium can

then be calculated in units which have the dimensions of conductance per cm^2. The sodium conductance per cm^2 is defined by

$$g_{Na} = I_{Na}/(V - V_{Na}), \quad (1)$$

where I_{Na} is the sodium current density (inward current positive), V is the displacement of the membrane potential from its resting value (depolarization negative), and V_{Na} is the equilibrium potential for the sodium ion (measured from the resting potential). In this expression the numerator on the right-hand side gives the flow of sodium ions and the denominator gives the driving force. Thus $V - V_{Na}$ is the work done in transferring $1/F$ mole of Na^+ from the inside to the outside of the fibre. A similar expression allows the potassium conductance (g_K) to be calculated from the potassium current (I_K) and the equilibrium potential for the potassium ion (V_K).

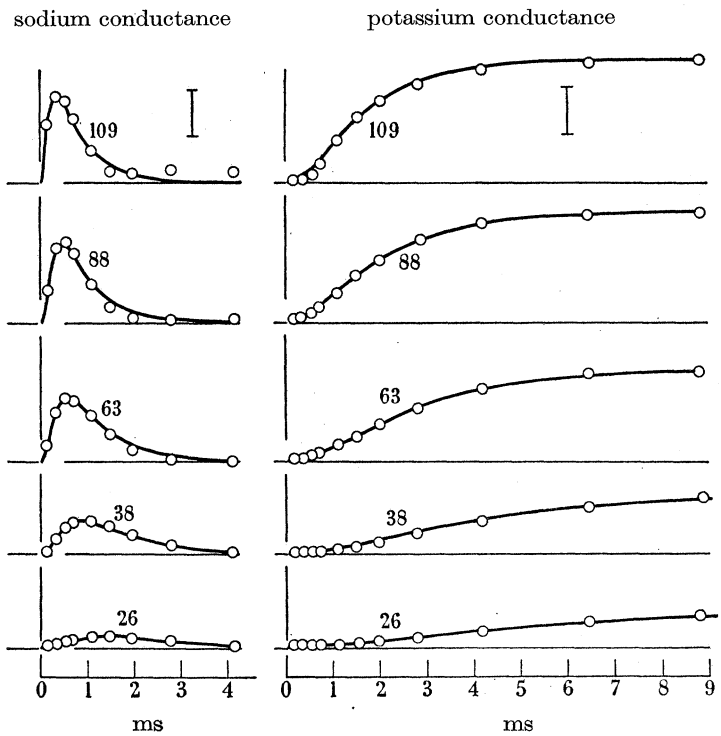

FIGURE 7. Changes in sodium and potassium conductance associated with different depolarizations at 6° C, replotted from Hodgkin & Huxley (1952*a*). The numbers attached to the curves give the depolarization in mV. The circles are experimental estimates and the smooth curves are solutions of equations used to describe these changes. The calibration lines at the top are 10 mmho/cm^2 and apply to all the curves.

Figure 7 shows a family of curves defining the changes in sodium and potassium conductance at different depolarizations. The circles are experimental estimates, and the smooth curves are solutions of fairly simple equations which may be used to describe the behaviour of the membrane. It will be seen that there is great variation in the magnitude and time course of the two conductances, but that

there is no sudden break or discontinuity, such as is often postulated in theories of nervous conduction. Before this set of curves can be applied to the action potential it is necessary to find out what happens when the membrane is repolarized. The result of such an experiment can be stated fairly simply. In all cases it is found that the conductance reverts to its resting value along a curve which is fairly close to an exponential. At 6° C (which was the temperature of the experiment in figure 7) the time constant of the restoration process for sodium is about 0·1 ms and for potassium about 6 ms. The process which leads to a decline of sodium conductance during a maintained depolarization is also reversed by repolarizing the membrane and has a time constant of about 10 ms at the resting potential if the temperature is 6° C.

The results in figure 7 suggest that depolarization causes a rapid but transient increase in sodium conductance and a delayed but maintained increase in potassium conductance. At first glance these changes appear too simple to account for the extremely varied reactions of a nerve fibre to electrical stimuli. We have therefore used our results to calculate the behaviour of a theoretical nerve under a variety of conditions. The example we shall consider is that of the propagated action potential.

A nerve fibre which is surrounded by a large volume of fluid obeys the well-known relation

$$\frac{a}{2R}\frac{\partial^2 V}{\partial x^2} = I, \tag{2}$$

where a is the radius of the fibre, R is the axoplasm resistivity, x is distance along the fibre, I is the membrane current density. This equation arises simply from the fact that the radial current through the membrane is given by the rate of change of longitudinal current with distance and that the latter is proportional to the potential gradient.

For steady propagation x may be replaced by $-\theta t$, where θ is the conduction velocity. Hence

$$\frac{a}{2R\theta^2}\frac{\mathrm{d}^2 V}{\mathrm{d}t^2} = I. \tag{3}$$

The membrane current I may be divided into a capacity current and into components carried by ions. In addition to the major components due to sodium and potassium ions there was evidence for a small residual or leakage current (I_L) due to other ions such as chloride. If this is included we have

$$\frac{a}{2R\theta^2}\frac{\mathrm{d}^2 V}{\mathrm{d}t^2} = C\frac{\mathrm{d}V}{\mathrm{d}t} + I_{\mathrm{Na}} + I_{\mathrm{K}} + I_L. \tag{4}$$

Using ionic conductances this becomes

$$\frac{a}{2R\theta^2}\frac{\mathrm{d}^2 V}{\mathrm{d}t^2} = C\frac{\mathrm{d}V}{\mathrm{d}t} + (V - V_{\mathrm{Na}})\,g_{\mathrm{Na}} + (V - V_{\mathrm{K}})\,g_{\mathrm{K}} + (V - V_L)\,g_L, \tag{5}$$

where g_L is the small leakage conductance and V_L is the membrane potential at which the leakage current is zero.

In equation (5), a, R, C, V_{Na}, V_K, V_L and g_L are constants which can be measured with reasonable accuracy. g_{Na} and g_K alter with time in a manner which depends on V. The nature of this variation is defined by the equations used to calculate curves such as those shown in figure 7. There is therefore sufficient information to solve equation (5) by numerical methods. Such a solution has recently been completed and is shown by the broken curve in figure 8. It agrees well with the action potential observed under comparable conditions. At the beginning of the computation the velocity θ is unknown. It can be found by guessing a value for θ and starting a trial solution with a small negative displacement of V. It is then

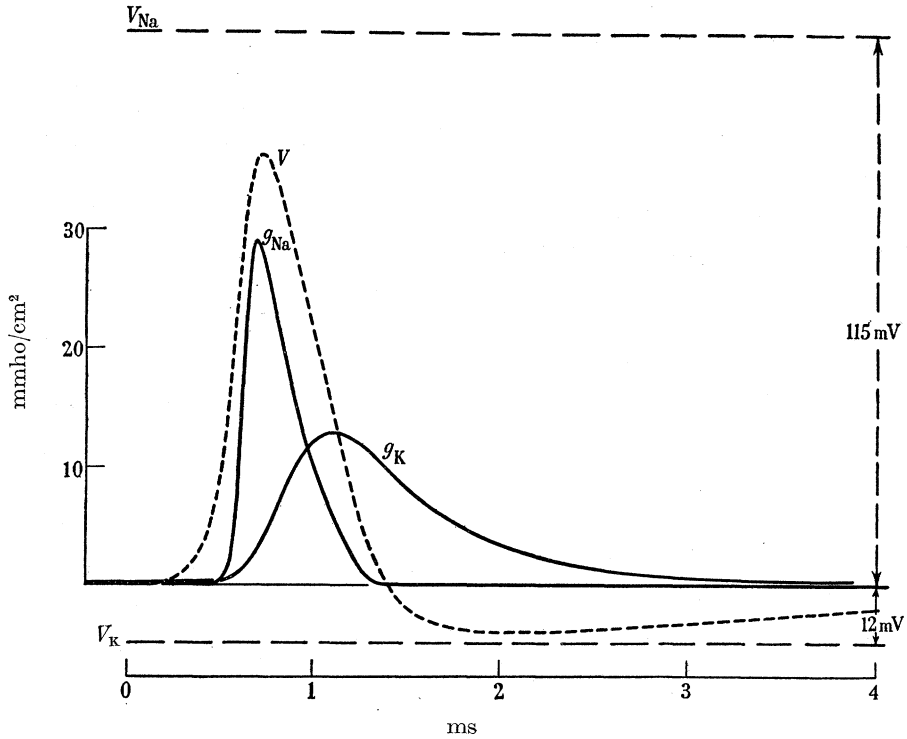

FIGURE 8. Theoretical action potential and conductance changes obtained by solving equation (5) numerically with subsidiary equations for g_{Na} and g_K given by Hodgkin & Huxley (1952*d*) using data appropriate to 18·5° C. Depolarization ($-V$) is plotted upward. Total entry $Na^+ = 4{\cdot}33$ $\mu\mu$mol/cm². Total exit $K^+ = 4{\cdot}26$ $\mu\mu$mol/cm².

found that V goes to $-\infty$ (depolarization) or to $+\infty$ according to whether the velocity is chosen too high or too low. These solutions correspond to action potentials which are accelerated or retarded by cathodes or anodes travelling faster or slower than the natural velocity of the fibre. The correct value of the velocity brings the potential back towards its resting value at the end of the run. The numerical calculation therefore predicts the form and velocity of the action potential with no arbitrary constants or scaling factors. The theoretical solution shown in figure 8 was obtained with numerical data appropriate to a 476 μ diameter fibre with an axoplasm resistivity of 35·4 Ω cm and a membrane capacity of 1·0 μF/cm² at a temperature of 18·5° C. The velocity observed on a fibre which

gave these measured values was 21·2 m/s, while that predicted by the numerical solution was 18·8 m/s.

Having done this analysis one can form a much clearer picture of the way in which an action potential propagates along a nerve fibre. In figure 8 the horizontal lines give the equilibrium potential for the potassium and sodium ions. At rest the potassium conductance is higher than the sodium conductance so that the potential is fairly near the potassium potential. When the fibre is depolarized by local circuits the internal potential rises, giving the foot of the action potential. After a short time the sodium conductance rises and sodium ions enter the fibre, thus depolarizing the membrane until its potential approaches the equilibrium potential for sodium. The potential does not remain at this level because the sodium conductance declines and the potassium conductance rises. This brings the potential down to the potassium potential and so gives a positive phase. The ionic conductances then revert to their resting value and the potential returns to its resting level. The state of the theoretical fibre is the same as before except that it has gained Na^+ and lost K^+. These quantities may be calculated from the theoretical curves in figure 8 and are found to agree reasonably with those observed by Keynes & Lewis (1951).

There is also satisfactory agreement between figure 8 and the change in membrane conductance observed by Cole & Curtis (1939). According to the theory we have outlined, the total membrane conductance is approximately equal to the sum of the sodium and potassium conductances and can therefore be obtained from $g_{Na}+g_K$. The resulting curve has approximately the same amplitude and shape as that found by Cole & Curtis.

The experiments and calculations discussed in this communication are described in detail by Hodgkin, Huxley & Katz (1952) and by Hodgkin & Huxley (1952*a*, *b*, *c*, *d*).

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The electric activity of the motor end-plate

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At the nerve-muscle junction, a specific process occurs which is not found during the propagation of impulses along nerve or muscle fibres; the nerve impulse causes acetylcholine (Ach) to be released from the motor nerve endings, and this