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CURRENTS CARRIED BY SODIUM AND POTASSIUM IONS THROUGH THE MEMBRANE OF THE GIANT AXON OF *LOLIGO*

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In the preceding paper (Hodgkin, Huxley & Katz, 1952) we gave a general description of the time course of the current which flows through the membrane of the squid giant axon when the potential difference across the membrane is suddenly changed from its resting value, and held at the new level by a feed-back circuit ('voltage clamp' procedure). This article is chiefly concerned with the identity of the ions which carry the various phases of the membrane current.

One of the most striking features of the records of membrane current obtained under these conditions was that when the membrane potential was lowered from its resting value by an amount between about 10 and 100 mV. the initial current (after completion of the quick pulse through the membrane capacity) was in the inward direction, that is to say, the reverse of the direction of the current which the same voltage change would have caused to flow in an ohmic resistance. The inward current was of the right order of magnitude, and occurred over the right range of membrane potentials, to be the current responsible for charging the membrane capacity during the rising phase of an action potential. This suggested that the phase of inward current in the voltage clamp records might be carried by sodium ions, since there is much evidence (reviewed by Hodgkin, 1951) that the rising phase of the action potential is caused by the entry of these ions, moving under the influence of concentration and potential differences. To investigate this possibility, we carried out voltage clamp runs with the axon surrounded by solutions with reduced sodium concentration. Choline was used as an inert cation since replacement of sodium with this ion makes the squid axon completely inexcitable, but does not reduce the resting potential (Hodgkin & Katz, 1949; Hodgkin, Huxley & Katz, 1949).

METHOD

The apparatus and experimental procedure are fully described in the preceding paper (Hodgkin *et al.* 1952). 'Uncompensated feed-back' was employed.

Sea water was used as a normal solution. Sodium-deficient solutions were made by mixing sea water in varying proportions with isotonic 'choline sea water' of the following composition:

Ion	g. ions/kg. H_2O	Ion	g. ions/kg. H_2O
$Choline^+$	484	Mg^{++}	54
K^+	10	Cl^-	621
Ca^{++}	11	HCO_3^-	3

The mixtures are referred to by their sodium content, expressed as a percentage of that in sea water (30% Na sea water, etc.).

RESULTS

Voltage clamps in sodium-free solution

Fig. 1 shows the main differences between voltage clamp records taken with the axon surrounded by sea water and by a sodium-free solution. Each record gives the current which crossed the membrane when it was depolarized by 65 mV. After the top record was made, the sea water surrounding the axon was replaced by choline sea water, and the middle record was taken. The fluid was again changed to sea water, and the bottom record taken. The amplifier gain was the same in all three records, but a given deflexion represents a smaller current in the choline solution, since the current was detected by the potential drop along a channel filled with the fluid which surrounded the axon, and the specific resistance of the choline sea water was about 23% higher than that of ordinary sea water.

The most important features shown in Fig. 1 are the following: (1) When the external sodium concentration was reduced to zero, the inward current disappeared and was replaced by an early hump in the outward current. (2) The late outward current was only slightly altered, the steady level being 15–20% less in the sodium-free solution. (3) The changes were reversed when sea water was replaced. The currents are slightly smaller in the bottom record than in the top one, but the change is not attributable to an action of the choline since a similar drop occurred when an axon was kept in sea water for an equal length of time.

A series of similar records with different strengths of depolarization is shown in Fig. 2. The features described in connexion with Fig. 1 are seen at all strengths between -28 and -84 mV. At the weakest depolarization (-14 mV.) the early phase of outward current in the sodium-free record is too small to be detected. At the highest strengths the early current is outward even in sea water, and is then increased in the sodium-free solution.

These results are in qualitative agreement with the hypothesis that the inward current is carried by sodium ions which, as an early result of the decrease in membrane potential, are permitted to cross the membrane in both

directions under a driving force which is the resultant of the effects of the concentration difference and the electrical potential difference across the membrane. When the axon is in sea water, the concentration of sodium outside the membrane $[Na]_o$ is 5–10 times greater than that inside, $[Na]_i$. This tends to make the inward flux exceed the outward. The electrical potential

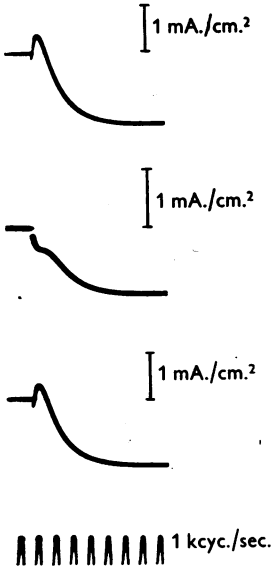

Fig. 1

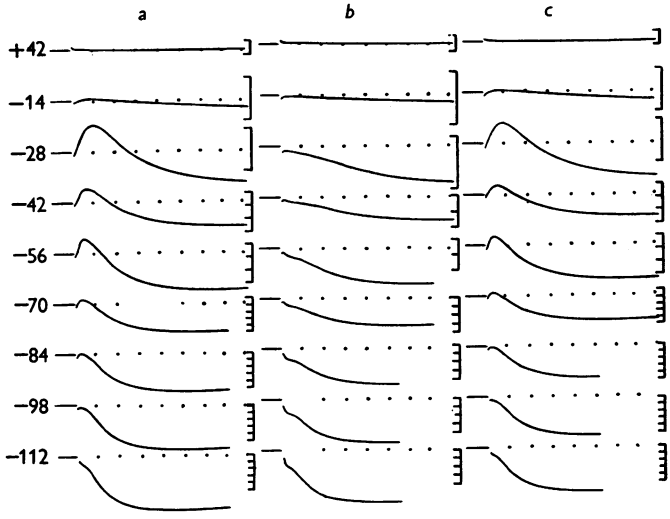

Fig. 2

Fig. 1. Records of membrane current during 'voltage clamps' in which membrane potential was lowered by 65 mV. Top record: axon in sea water. Centre record: axon in choline sea water. Bottom record: after replacing sea water. Axon no. 15; temperature 11° C. Inward current is shown upwards in this and all other figures.

Fig. 2. Records of membrane current during 'voltage clamps'. *a*, axon in sea water; *b*, axon in choline sea water; *c*, after replacing sea water. Displacement of membrane potential indicated in mV. Axon no. 21; temperature 8·5° C. Vertical scale: 1 division is 0·5 mA./cm.². Horizontal scale: interval between dots is 1 msec.

difference E also helps the inward and hinders the outward flux so long as it is positive, i.e. in the same direction as the resting potential. The net current carried by the positive charge of the sodium ions is therefore inward unless the depolarization is strong enough to bring E to a sufficiently large negative value to overcome the effect of the concentration difference. The critical value of E at which the fluxes are equal, and the net sodium current is therefore zero, will be called the 'sodium potential', E_{Na}. Its value should be given by the Nernst equation

$$E_{Na} = \frac{RT}{F} \log_e \frac{[Na]_i}{[Na]_o}. \qquad (1)$$

With values of E more negative than this, the net sodium flux is outward, causing the early phase of the outward current seen in the lowest record of the first and third columns of Fig. 2, where the axon was in sea water and was depolarized by 112 mV. A family of voltage clamp records which shows particularly well this transition from an initial rise to an initial fall as the strength of depolarization is increased is reproduced as Fig. 14 of the preceding paper.

When the axon is placed in a sodium-free medium, such as the 'choline sea water', there can be no inward flux of sodium, and the sodium current must always be outward. This will account for the early hump on the outward current which is seen at all but the lowest strength of depolarization in the centre column of Fig. 2.

Voltage clamps with reduced sodium concentration

The results of reducing the sodium concentration to 30 and 10% of the value in sea water are shown in Figs. 3 and 4 respectively. These figures do not show actual records of current through the membrane. The curves are graphs of ionic current against time, obtained by subtracting the current through the capacity from the recorded total current. The initial surge in an anodal record was assumed to consist only of capacity current, and the capacity current at other strengths was estimated by scaling this in proportion to the amplitude of the applied voltage change.

As would be expected, the results are intermediate between those shown in Fig. 2 for an axon in sea water and in choline sea water. Inward current is present, but only over a range of membrane potentials which decreases with the sodium concentration, and within that range, the strength of the current is reduced. A definite sodium potential still exists beyond which the early hump of ionic current is outward, but the strength of depolarization required to reach it decreases with the sodium concentration. Thus, in the first column of Fig. 3, with the axon in 30% sodium sea water, the sodium potential is almost exactly reached by a depolarization of 79 mV. In the second column, with sea water surrounding the axon, the sodium potential is just exceeded by a depolarization of 108 mV. In column 3, after re-introducing 30% sodium sea water, the sodium potential is slightly exceeded by a depolarization of 79 mV. Similarly, in Fig. 4, the sodium potentials are almost exactly reached by depolarizations of 105, 49 and 98 mV. in the three columns, the axon being in sea water, 10% sodium sea water and sea water respectively. The sequence of changes in the form of the curves as the sodium potential is passed is remarkably similar in all cases.

The external sodium concentration and the 'sodium potential'

Estimation of the 'sodium potential' in solutions with different sodium concentrations is of particular importance because it leads to a quantitative

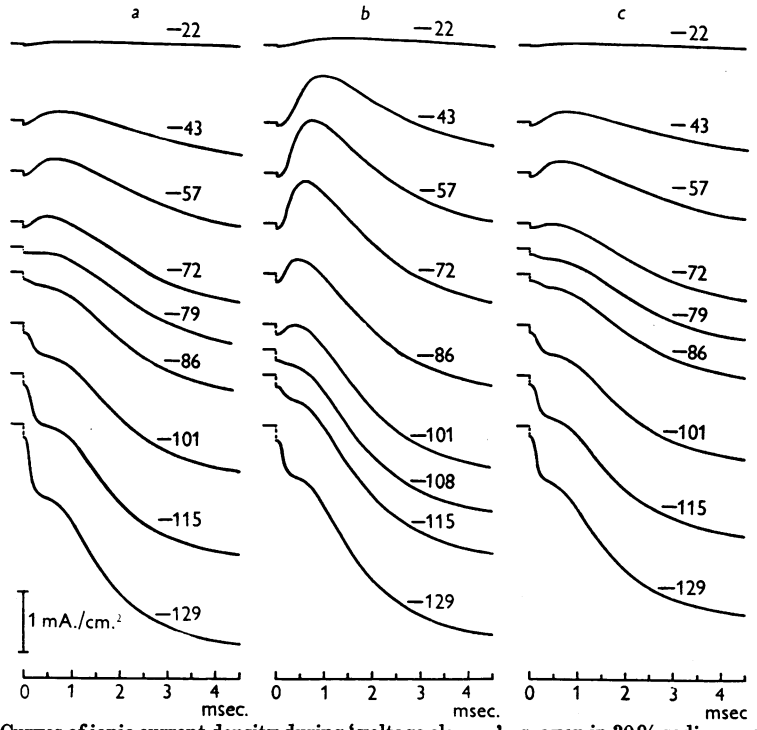

Fig. 3. Curves of ionic current density during 'voltage clamps'. *a*, axon in 30% sodium sea water; *b*, axon in sea water; *c*, after replacing 30% sodium sea water. Displacement of membrane potential indicated in millivolts. Axon no. 20; temperature 6·3° C.

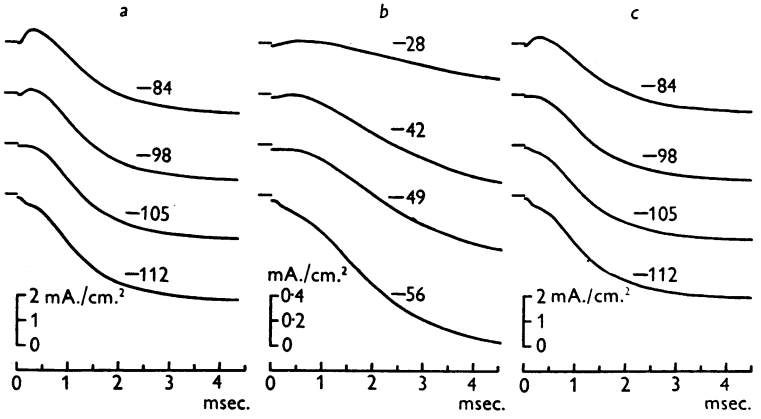

Fig. 4. Curves of ionic current density during voltage clamps in neighbourhood of sodium potential. *a*, axon in sea water; *b*, axon in 10% sodium sea water; *c*, after replacing sea water. Note that ordinate scale is larger in *b* than in *a* and *c*. Displacement of membrane potential in millivolts indicated for each curve. Axon no. 21; temperature 8·5° C.

test of our hypothesis. Equation (1) gives the sodium potential in sea water (E_{Na}), and the corresponding quantity (E'_{Na}) when the external sodium concentration is reduced to $[Na]'_o$ is given by

$$E'_{Na} = \frac{RT}{F} \log_e \frac{[Na]_i}{[Na]'_o}.$$

Hence $$E'_{Na} - E_{Na} = \frac{RT}{F}\left\{\log_e \frac{[Na]_i}{[Na]'_o} - \log_e \frac{[Na]_i}{[Na]_o}\right\} = \frac{RT}{F} \log_e \frac{[Na]_o}{[Na]'_o}. \quad (2)$$

The displacements of membrane potential, V, corresponding to these values are $V_{Na} = E_{Na} - E_r$ and $V'_{Na} = E'_{Na} - E'_r$, where E_r and E'_r are the values of the resting potential in sea water and in the test solution respectively. Hence

$$(V'_{Na} - V_{Na}) + (E'_r - E_r) = \frac{RT}{F} \log_e \frac{[Na]_o}{[Na]'_o}. \quad (3)$$

Each term in this equation can be determined experimentally, and data were obtained in four experiments on two axons. The results are given in Table 1, where the observed shift in sodium potential is compared with that predicted from the change in sodium concentration by Equation (3). It will be

TABLE 1. Comparison of observed and theoretical change in sodium potential when the fluid surrounding an axon is changed from sea water to a low sodium solution. Observed change: $E'_{Na} - E_{Na} = (V'_{Na} - V_{Na}) + (E'_r - E_r)$; theoretical change $= \frac{RT}{F} \log_e \frac{[Na]_o}{[Na]'_o}$.

Axon no.	Temp. (° C.)	$\frac{[Na]'_o}{[Na]_o}$	V_{Na} (mV.)	V'_{Na} (mV.)	$(E'_r - E_r)$ (mV.)	Sodium potential shift: Observed (mV.)	Sodium potential shift: Theoretical (mV.)
20	6·3	0·3	−105	−78	+3	+30	+28·9
20	6·3	0·1	−96	−45	+4	+55	+55·3
21	8·5	0·1	−100	−48	+4	+56	+55·6
21	8·5	0·1	−95	−45	+4	+54	+55·6

seen that there is good agreement, providing strong evidence that the early rise or fall in the recorded ionic current is carried by sodium ions, moving under the influence of their concentration difference and of the electric potential difference across the membrane.

Details of the estimation of the quantities which enter into Equation (3) are given in the following paragraphs.

Determination of V_{Na}. At the sodium potential there is neither inward sodium current, shown by an initial rise in the ionic current, nor outward sodium current, shown by an early hump in the outward current. It was found that these two criteria did in fact define the sodium potential very sharply, i.e. a hump appeared as soon as the ionic current showed an initial fall. It was therefore permissible to take as V_{Na} the strength of depolarization which gave an ionic current curve which started horizontally. This criterion was much more convenient to apply than the absence of a hump, since records were taken at fairly wide intervals of V (usually 7 mV.) and an interpolation procedure was necessary in order to estimate V_{Na} to the nearest 0·5 mV.

Change in resting potential. Experiments with ordinary capillary internal electrodes showed that the resting potential increased on the average by 4 mV. when the sea water surrounding the axon was replaced by choline sea water (a correction of 1·5 mV. for junction potentials in the external solutions is included in this figure). With intermediate sodium concentrations, the change in resting potential was assumed to be proportional to the change in sodium concentration. For instance, the resting potential in 30% sodium sea water was taken as 2·8 mV. higher than that in sea water.

Slow change in condition of axon. When an axon is kept in sea water, its sodium content rises (Steinbach & Spiegelman, 1943; Keynes & Lewis, 1951) and its resting potential falls. Both of these effects bring E_r and E_{Na} closer together, diminishing the absolute magnitude of V_{Na}. In comparing V_{Na} in two solutions, it was therefore necessary to determine V_{Na} first in one solution, then in the other and finally in the first solution again. The second value of V_{Na} was then compared with the mean of the first and third.

The internal sodium concentration and the sodium potential

In freshly mounted fibres the average difference between the sodium potential and the resting potential was found to be -109 mV. (ten axons with a range of -95 to -119 mV. at an average temperature of 8° C.). The average resting potential in these fibres was 56 mV. when measured with a microelectrode containing sea water. By the time the sodium potential was measured the resting potential had probably declined by a few millivolts and may be taken as 50 mV. Allowing 10–15 mV. for the junction potential between sea water and axoplasm (Curtis & Cole, 1942; Hodgkin & Katz, 1949) this gives an absolute resting potential of 60–65 mV. The absolute value of the sodium potential would then be -45 to -50 mV. The sodium concentration in sea water is about 460 m.mol./kg. H_2O (Webb, 1939, 1940) so that the internal concentration of sodium would have to be 60–70 m.mol./kg. H_2O in order to satisfy Equation 1. This seems to be a very reasonable estimate since the sodium concentration in freshly dissected axons is about 50 m.mol./kg. H_2O while that in axons kept for 2 or 3 hr. is about 100 m.mol./kg. H_2O (Steinbach & Spiegelman, 1943; Keynes & Lewis, 1951; Manery, 1939, for fraction of water in axoplasm).

Outward currents at long times

So far, this paper has been concerned with the earliest phases of the membrane current that flows during a voltage clamp. The only current which has the opposite sign from the applied voltage pulse is the inward current which occurs over a certain range of depolarizations when the surrounding medium contains sodium ions. This inward current is always transient, passing over into outward current after a time which depends on the strength of depolarization and on the temperature. The current at long times resembles that in an ohmic resistance in having the same sign as the applied voltage change, but differs in that the outward current due to depolarization rises with a delay to a density which may be 50–100 times greater than that associated with a similar increase in membrane potential. Figs. 1–3 show that this late current

is not greatly affected by the concentration of sodium in the fluid surrounding the axon.

An outward current which arises with a delay after a fall in the membrane potential is clearly what is required in order to explain the falling phase of the action potential. The outward currents reached in a voltage clamp may considerably exceed the maximum which occurs in an action potential; this may well be because the duration of an action potential is not sufficient to allow the outward current to reach its maximum value. These facts suggest that the outward current associated with prolonged depolarization is the same current which causes the falling phase of the action potential. The evidence (reviewed by Hodgkin, 1951) that the latter is caused by potassium ions leaving the axon is therefore a suggestion that the former is also carried by potassium ions. Direct evidence that such long-continued and outwardly directed membrane currents are carried by potassium ions has now been obtained in *Sepia* axons by a tracer technique (unpublished experiments). We shall therefore assume that this delayed outward current is carried by potassium ions, and we shall refer to it as 'potassium current', I_K. Since it is outward, it is not appreciably affected by the external potassium concentration, and evidence for or against potassium being the carrier cannot easily be obtained by means of experiments analogous to those which have just been described with altered external sodium concentration.

I_K in sea water and choline. As has been mentioned, the later part of the current record during a constant depolarization is much the same whether the axon is surrounded by sea water or by one of the solutions with reduced sodium concentration. There are, however, certain differences. For a given strength of depolarization, the maximum outward current is smaller by some 10 or 20% in the low-sodium solution, and at the higher strengths where the outward current is not fully maintained, the maximum occurs earlier in the low-sodium solution. Part of the difference in amplitude is explained by the difference of resting potential. Since the resting potential is greater in the low-sodium medium, a higher strength of depolarization is needed to reach a given membrane potential during the voltage clamp. This difference can be allowed for by interpolation between the actual strengths employed in one of the solutions. In most cases, this procedure did not entirely remove the difference between the amplitudes. There are, however, two other effects which are likely to contribute. In the first place, the effect of not using 'compensated feed-back' is probably greater in the low-sodium solution (see preceding paper, p. 445). This further reduces the amplitude of the voltage change which actually occurs across the membrane. In the second place, the fact that the current reached its maximum earlier suggests that 'polarization' (preceding paper, p. 445) had a greater effect in the low-sodium solution. We do not know enough about either of these effects to estimate the amount by

which they may have reduced the potassium current. It does seem at least possible that they account for the whole of the discrepancy, and we therefore assume provisionally that substituting choline sea water for sea water has no direct effect on the potassium current.

Separation of ionic current into I_{Na} and I_K

The results so far described suggest that the ionic current during a depolarization consists of two more or less independent components in parallel, an early transient phase of current carried by sodium ions, and a delayed long-lasting phase of current carried by potassium ions. In each case, the direction of the current is determined by the gradient of the electro-chemical potential of the ion concerned. It will clearly be of great interest if it is possible to estimate separately the time courses of these two components. There is enough information for doing this in data such as are presented in Fig. 2, if we make certain assumptions about the effect of changing the solution around the axon. If we compare the currents when the axon is in the low-sodium solution with those in sea water, the membrane potential during the voltage clamp being the same in both cases, then our assumptions are:

(1) The time course of the potassium current is the same in both cases.

(2) The time course of the sodium current is similar in the two cases, the amplitude and sometimes the direction being changed, but not the time scale or the form of the time course.

(3) $\frac{dI_K}{dt}=0$ initially for a period about one-third of that taken by I_{Na} to reach its maximum.

The first two of these assumptions are the simplest that can be made, and do not conflict with any of the results we have described, while the third is strongly suggested by the form of records near the sodium potential, as pointed out on p. 454. These points are sufficient reason for trying this set of assumptions first, but their justification can only come from the consistency of the results to which they lead. The differences between the effects of lack of compensation, and of the polarization phenomenon, in the two solutions, referred to at the end of the last section, will of course lead to certain errors in the analysis in the later stages of the ionic current.

The procedure by which we carried out this analysis was as follows:

(1) Three series of voltage clamp records at a range of strengths were taken, the first with the axon in one of the solutions chosen for the comparison, the second with the axon in the other solution, and the third with the first solution again. Such a set of records is reproduced in Fig. 2.

(2) Each record was projected on to a grid in which the lines corresponded to equal intervals of time and current, and the current was measured at a series of time intervals after the beginning of the voltage change.

(3) The time course of the initial pulse of current through the membrane capacity was determined from anodal records as described on p. 452 above, and subtracted from the measured total currents. Different corrections were needed in the two solutions, because the capacity current had a slower time course in the low sodium solutions, perhaps as a result of their lower conductivity. This procedure yielded a family of curves of ionic current against time such as is shown in Fig. 3.

(4) Each pair of curves in the first and third series at the same strength was averaged, in order to allow for the slow deterioration in the condition of the axon that took place during the experiment.

(5) The difference in resting potential was allowed for by interpolating between consecutive curves in either the second series or the series of averaged curves.

(6) We have now obtained curves of ionic current against time in the two solutions, with strengths of depolarization which reach the same membrane potential during the voltage clamp. The ionic current will be called I_i in sea water and I'_i in the low-sodium solution. The components carried by sodium and potassium in the two cases will be called I_{Na}, I'_{Na}, I_K and I'_K respectively. The next step was to plot I'_i against I_i, and to measure the initial slope k of the resulting graph (corresponding to the beginning of the voltage clamp).

Since we assume that initially $dI_K/dt=0$, and that I_{Na} and I'_{Na} have similar time courses, $k=I'_{Na}/I_{Na}$. Further, since we assume that $I_K=I'_K$,

$$I_i-I'_i=I_{Na}-I'_{Na}=I_{Na}(1-k).$$

Hence
$$I_{Na}=(I_i-I'_i)/(1-k), \tag{4}$$

$$I'_{Na}=k(I_i-I'_i)/(1-k), \tag{5}$$

and
$$I_K=I'_K=I_i-I_{Na}=(I'_i-kI_i)/(1-k). \tag{6}$$

These equations give the values of the component currents at any time in terms of the known quantities I_i and I'_i at that time. Curves of I_{Na} and I_K against time could therefore be constructed by means of these equations.

This procedure is illustrated in Fig. 5, which shows two pairs of ionic current curves together with the deduced curves of I_{Na}, I'_{Na} and I_K against time. The complete family of I_K curves from this experiment is shown in Fig. 6*b*, while Fig. 6*a* shows the family derived by the same procedure from another experiment. A satisfactory feature of these curves, which is to some extent a check on the validity of the assumptions, is that the general shape is the same at all strengths. If the time courses of I_{Na} and I'_{Na} had not been of similar form, Equation (6) would not have removed sodium current correctly. It would then have been unlikely that the curve of potassium current at a potential away from the sodium potential would have been similar to that at the sodium potential, where the sodium current is zero and Equation (6) reduces to $I_K=I_i$ because $k=\infty$.

On the other hand, it is clearly inconsistent that the I_{Na} and I'_{Na} curves in the lower part of Fig. 5 reverse their direction at 2 msec. after the beginning of the pulse. This is a direct consequence of the fact, discussed on p. 456 above, that the late outward current is somewhat greater in sea water than in the low-sodium solutions, even when allowance is made for the resting potential shift.

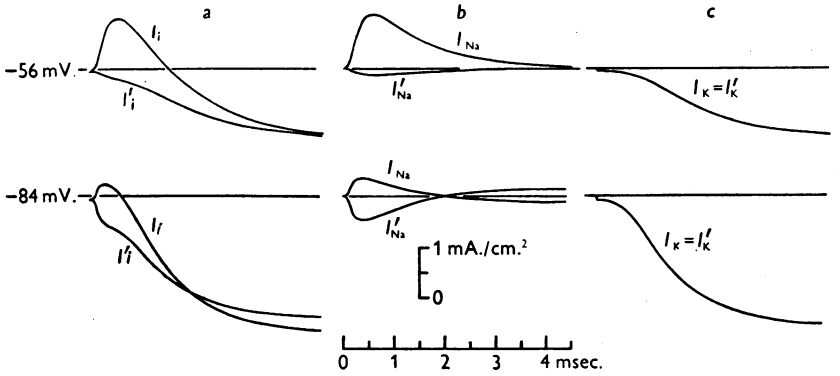

Fig. 5. Curves illustrating separation of ionic current into I_{Na} and I_K. Upper part of figure. *a*, ionic currents: I_i, axon in sea water, membrane potential lowered by 56 mV.; I'_i, axon in 10% sodium sea water, membrane potential lowered by 60 mV. (average of curves taken before and after I_i). *b*, sodium currents: I_{Na}, sodium current in sea water; I'_{Na}, sodium current in 10% sodium sea water. *c*, potassium current, same in both solutions. Lower part of figure. Same, but membrane potential lowered by 84 mV. in sea water and 88 mV. in 10% sodium sea water. Current and time scales same for all curves. Axon no. 21; temperature 8·5° C.

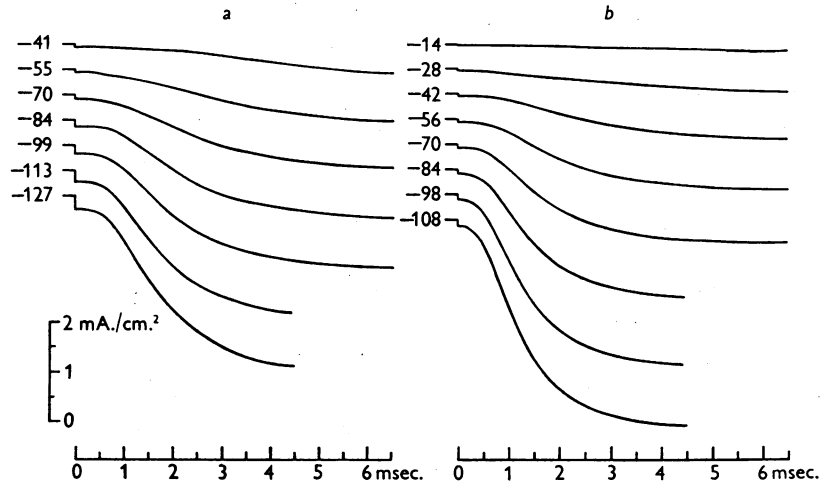

Fig. 6. Curves of potassium current against time for various strengths of depolarization. Displacement of membrane potential when axon is in sea water is indicated for each curve, in millivolts. *a*, derived from voltage clamps with axon in 30% sodium sea water, sea water and 30% sodium sea water. Axon no. 20; temperature 6·3° C. *b*, derived from voltage clamps with axon in 10% sodium sea water, sea water and 10% sodium sea water. Axon no. 21; temperature 8·5° C.

It was pointed out there that the difference may well be due to lack of compensation and to 'polarization'. Until these effects can be eliminated, estimates of sodium current at the longer times will be quite unreliable, and the corresponding estimates of potassium current will be somewhat reduced by these errors.

All the sodium current curves agree in showing that I_{Na} rises to a peak and then falls. With weak depolarizations (less than 40 mV.) the steady state value is definitely in the same direction as the peak, but at higher strengths the measured I_{Na} tends to a value which may have either direction. Since the sources of error mentioned in the last paragraph can cause an apparent reversal of I_{Na} during the pulse, it is possible that if these errors were larger than we suppose the whole of the apparent drop of I_{Na} from its peak value might also be spurious. At the time that an account of preliminary work with this technique was published (Hodgkin *et al.* 1949) we were unable to decide this point, and assumed provisionally that I_{Na} did not fall after reaching its maximum value. We are now convinced that this fall is genuine: (1) because of improvements in technique; (2) because of further experiments of other kinds which are described in the next two papers of this series (Hodgkin & Huxley, 1952*a*, *b*); and (3) because we occasionally observed records of the kind shown in Fig. 7. This is a record of membrane current during a voltage clamp in which an axon in choline sea water was depolarized by 84 mV. It will be seen that the early hump of outward current (due to sodium ions) was so marked that the total current reached a maximum at about 0·2 msec. and then fell before finally rising to the plateau attributable to movement of potassium ions. Unless we make the quite unwarrantable assumption that I_K itself has this double-humped form, this curve can only be explained by supposing that I_{Na} (outward in this case) falls after passing through a maximum value. The fact that such a clear maximum was not regularly observed was no doubt due to I_{Na} usually being smaller in relation to I_K than in this case.

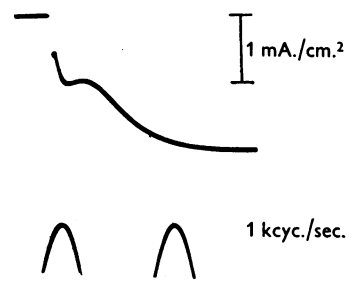

Fig. 7. Record of membrane current during a voltage clamp with axon in choline sea water, showing early maximum of outward current. Displacement of membrane potential during clamp = −84 mV. Axon no. 24; temperature 20° C.

We do not present a family of I_{Na} curves here, because the sequence of the curves is interrupted at the sodium potential. For this reason, the information is better given in the curves of 'sodium conductance' which are derived later in this paper (pp. 461–2 and Fig. 8). The variation of peak sodium current with strength of depolarization is shown in Fig. 13 for axons both in sea water and in low-sodium solutions.

Current carried by other ions. It seems to be possible to account for the variation of current with time during the voltage clamp by variations in the currents carried across the membrane by two ions, namely sodium and potassium. If, however, the membrane allowed constant fluxes of one or more other ion species, the current carried by these would form part of the 'I_K' which is deduced by our procedure, since this current would be independent both of time and of sodium concentration, and I_K is defined by its satisfying these criteria during the earliest part of the pulse. Reasons will be given in the next paper (Hodgkin & Huxley, 1952*a*) for supposing that the current carried by other ions is appreciable, though not of great importance except when the membrane potential is near to or above its resting value. Each of the I_K curves in Figs. 5 and 6 therefore includes a small constant component carried by other ions. This component probably accounts for much of the step in 'I_K' at the beginning of the voltage pulse.

Expression of ionic currents in terms of conductances

General considerations. The preceding sections have shown that the ionic current through the membrane is chiefly carried by sodium and potassium ions, moving in each case under a driving force which is the resultant of the concentration difference of the ion on the two sides of the membrane, and of the electrical potential difference across the membrane. This driving force alone determines the direction of the current carried by each ionic species, but the magnitude of the current depends also on the freedom with which the membrane allows the ions to pass. This last factor is a true measure of the 'permeability' of the membrane to the ion species in question. As pointed out by Teorell (1949*a*), a definition of permeability which takes no account of electrical forces is meaningless in connexion with the movements of ions, though it may well be appropriate for uncharged solutes.

The driving force for a particular ion species is clearly zero at the equilibrium potential for that ion. The driving force may therefore be measured as the difference between the membrane potential and the equilibrium potential. Using the same symbols as in Equations (1)–(3), the driving force for sodium ions will be $(E-E_{Na})$, which is also equal to $(V-V_{Na})$. The permeability of the membrane to sodium ions may therefore be measured by $I_{Na}/(E-E_{Na})$. This quotient, which we denote by g_{Na}, has the dimensions of a conductance (current divided by potential difference), and will therefore be referred to as the sodium conductance of the membrane. Similarly, the permeability of the membrane to potassium ions is measured by the potassium conductance g_K, which is defined as $I_K/(E-E_K)$. Conductances defined in this way may be called chord conductances and must be distinguished from slope conductances (G) defined as $\partial I/\partial E$.

These definitions are valid whatever the relation between I_{Na} and $(E-E_{Na})$,

or between I_K and $(E-E_K)$, but the usefulness of the definitions, and the degree to which they measure real properties of the membrane, will clearly be much increased if each of these relations is a direct proportionality, so that g_{Na} and g_K are independent of the strength of the driving force under which they are measured. It will be shown in the next paper (Hodgkin & Huxley, 1952*a*) that this is the case, for both sodium and potassium currents, in an axon surrounded by sea water, when the measurement is made so rapidly that the condition of the membrane has no time to change.

Application to measured sodium and potassium currents. The determination of sodium current, potassium current and sodium potential have been described in earlier sections of the present paper. The method by which the potassium potential, E_K, was found is described in the next paper (Hodgkin & Huxley, 1952*a*), and the values used here are taken from that paper. We have

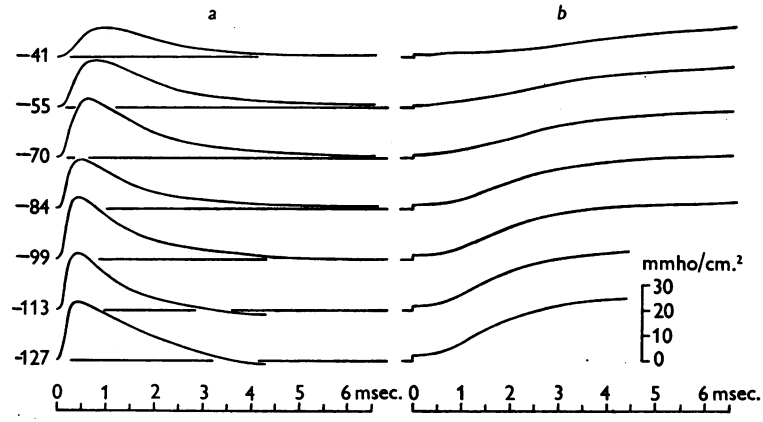

Fig. 8. Curves of sodium conductance (*a*) and potassium conductance (*b*). Displacement of membrane potential (millivolts) when axon was in sea water is indicated on each curve. Curves of I_i and I_K in same experiment are shown in Figs. 3 and 6*a* respectively. Axon no. 20; temperature 6·3° C.

therefore sufficient data to estimate g_{Na} and g_K as functions of time during a voltage clamp. Families of g_{Na} and g_K curves, for various strengths of depolarization, are shown in Fig. 8. The sodium conductances are calculated from the sodium currents in sea water, divided by the difference between membrane potential and sodium potential in sea water. If the same procedure had been applied to the corresponding quantities in the low-sodium solution, a similar family would have been obtained, but the relative amplitudes of the members of the family would have been slightly different. The values obtained from the sea water figures are the more interesting, both because they refer to a more normal condition, and because it is only in this case that the instantaneous relation between sodium current and voltage is linear

(Hodgkin & Huxley, 1952*a*). The corresponding distinction does not arise with g_K, since both I_K and E_K are the same in both solutions.

The shapes of individual curves in Fig. 8 are of course similar to those of curves of I_{Na} or I_K, such as are shown in Figs. 5 and 6, since the driving force for each ion is constant during any one voltage clamp. The change of amplitude of the curves with strength of depolarization is, however, less marked than with the current curves. For potassium, this can be seen by comparing Figs. 6*a* and 8*b*, which refer to the same experiment. For sodium, it is clear from Fig. 8*a* that the conductance curves undergo no marked change at the sodium potential, while the current curves reverse their direction at this point.

Membrane potential and magnitude of conductance. The effect of strength of depolarization on the magnitude of the conductances is shown in Figs. 9 and 10. For each experiment, the maximum values of g_{Na} and g_K reached in a voltage clamp of strength about 100 mV. are taken as unity, and the maximum values at other strengths are expressed in terms of these. Values of g_{Na} are available only from the four experiments in which there were enough data in sea water and in a low-sodium solution for the complete analysis to be carried out. The maximum values of g_K were also estimated in two other experiments. This was possible without complete analysis because the late current was almost entirely carried by potassium when the axon was in choline sea water.

The two curves are very similar in shape. At high strengths they become flat, while at low strengths they approach straight lines. Since the ordinate is plotted on a logarithmic scale, this means that peak conductance increases exponentially with strength of depolarization. The asymptote approached by the sodium conductances is probably steeper than that of the potassium data; the peak sodium conductances increase e-fold for an increase of 4 mV. in strength of depolarization; for potassium the corresponding figure is 5 mV.

The values of conductance at a depolarization of 100 mV., which are represented as unity in Figs. 9 and 10, are given in Table 2. In all these cases where enough measurements were made to construct a curve, the axon had been used for other observations before we took the records on which the analysis is based. In several cases, it was possible to estimate one or two values of sodium and potassium peak conductance at the beginning of the same experiment, and these were considerably higher than the corresponding values in Table 2, which must therefore be depressed by deterioration of the fibres.

More representative values of the peak g_K and g_{Na} at high strengths were estimated at the beginning of experiments on several fibres. Potassium current at long times can be estimated without difficulty, since I_{Na} is then negligible, especially at these depolarizations which are near the sodium potential. Nine fibres at 3–11° C. gave peak values of g_K at -100 mV. ranging from 22 to 41 m.mho/cm.^{2}, with a mean of 28; five fibres at 19–23° C. gave a range of

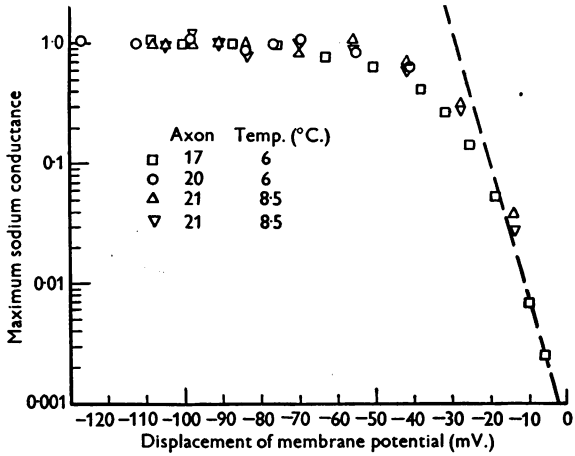

Fig. 9. Maximum sodium conductance reached during a voltage clamp. Ordinate: peak conductance relative to value reached with depolarization of 100 mV., logarithmic scale. Abscissa: displacement of membrane potential from resting value (depolarization negative).

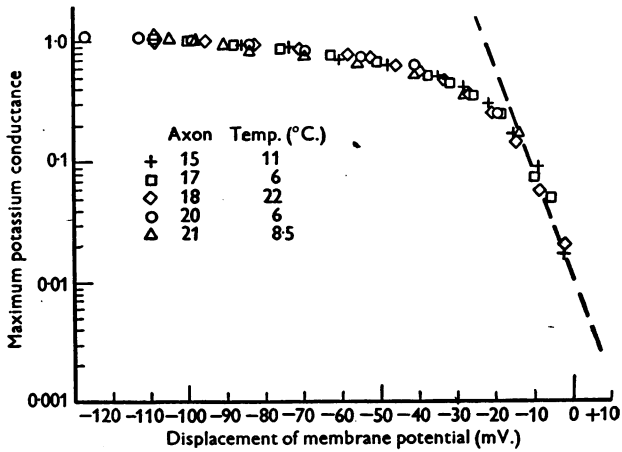

Fig. 10. Maximum potassium conductance reached during a voltage clamp. Ordinate: maximum conductance relative to value reached with depolarization of 100 mV., logarithmic scale. Abscissa: displacement of membrane potential from resting value (depolarization negative).

TABLE 2. Peak values of sodium and potassium conductance at a depolarization of 100 mV. Same experiments as Figs. 9 and 10. In each case, the value given in this table is represented as unity in Fig. 9 or Fig. 10.

		Peak conductances at −100 mV.	
Axon no.	Temp. (° C.)	Sodium (m.mho/cm.²)	Potassium (m.mho/cm.²)
15	11	—	21
17	6	18	20
18	21	—	28
20	6	22	23
21	8·5	23	31
21	8·5	17	—
		Mean 20	25

33–37 m.mho/cm.^{2}, mean 35. Values of the peak sodium conductance were obtained by measuring the peak inward current at a depolarization of about 60 mV. and dividing by the corresponding value of $(V - V_{Na})$. They are probably 10–20% low because current carried by potassium and other ions makes the peak inward current less than the peak sodium current, and because the peak conductance at 60 mV. depolarization is slightly less than that reached at 100 mV. Five fibres at 3–9° C. gave values ranging from 22 to 48 m.mho/cm.^{2}, mean 30; a single fibre at 22° C. gave 24 m.mho/cm.^{2}.

These results show that both g_K and g_{Na} can rise considerably higher than the values for the fully analysed experiments given in Table 2. They may be summarized by saying that on the average a freshly mounted fibre gives maximum conductances of about 30–35 m.mho/cm.^{2} both for sodium and for potassium, corresponding to resistances of about 30 Ω. for 1 cm.^{2} of membrane. This value may be compared with the resting resistance of about 1000 Ω. cm.^{2} (Cole & Hodgkin, 1939), and the resistance at the peak of an action potential, which is about 25 Ω. cm.^{2} (Cole & Curtis, 1939).

Membrane potential and rate of rise of conductance. It is evident from Fig. 8 that the strength of depolarization affects not only the maximum values attained by g_{Na} and g_K during a voltage clamp, but also the rates at which these maxima are approached. This is well shown by plotting the maximum rate of rise of conductance against displacement of membrane potential. This has been done for sodium conductance in Fig. 11 and for potassium conductance in Fig. 12. The data for g_K were taken from a fully analysed run, but in the case of sodium it is sufficient to take the maximum rate of rise of total ionic current, with the axon in sea water, and divide by $(V - V_{Na})$. The maximum rate of rise occurs so early that dI_K/dt is still practically zero, so that $dI_i/dt = dI_{Na}/dt$.

These graphs show that the rates of rise of both conductances continue to increase as the strength of the depolarization is increased, even beyond the point where the maximum values reached by the conductances themselves have become practically constant.

DISCUSSION

Only two aspects of the results described in this paper will be discussed at this stage. The first is the relationship between sodium current and external sodium concentration; the second is the application of the results to the interpretation of the action potential. Further discussion will be reserved for the final paper of this series (Hodgkin & Huxley, 1952*c*).

Sodium current and external sodium concentration

General considerations and theory. We have shown in the earlier parts of this paper that there is good reason for believing that the component of membrane

current that we refer to as I_{Na} is carried by sodium ions which move down their own electrochemical gradient, the speed of their movement, and therefore the magnitude of the current, being also determined by changes in the freedom

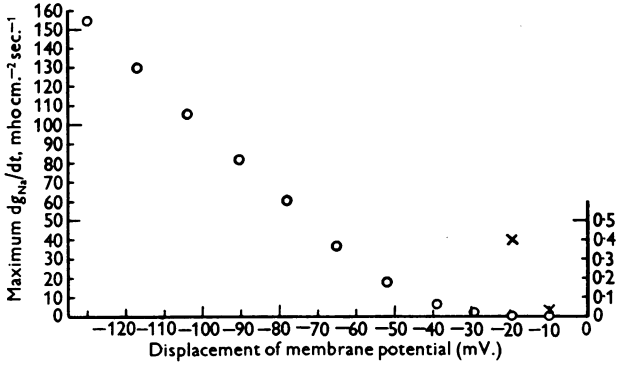

Fig. 11. Maximum rates of rise of sodium conductance during voltage clamps plotted against displacement of membrane potential. Circles are to be read with the scale on the left-hand side. The two lowest points are also re-plotted as crosses on 100 times the vertical scale, and are to be read with the scale on the right-hand side. The peak sodium conductance reached at high strengths of depolarization was 16 m.mho/cm.^{2}. Axon no. 41; temperature 3·5° C. Compensated feed-back.

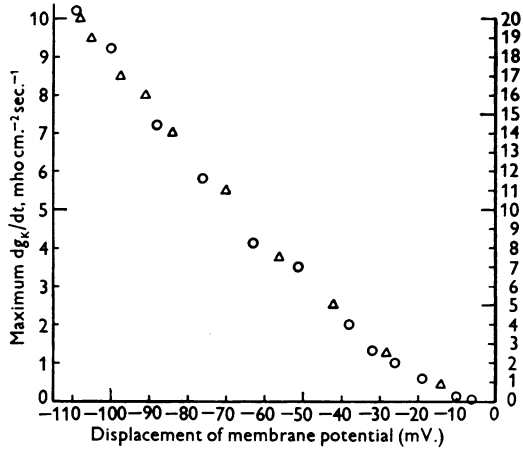

Fig. 12. Maximum rates of rise of potassium conductance during voltage clamps, plotted against displacement of membrane potential. Circles, left-hand scale: axon no. 17; temperature 6° C. Triangles, right-hand scale: axon no. 21; temperature 8·5° C. At −100 mV. the maximum potassium conductance was 20 m.mho/cm.^{2} for axon no. 17 and 31 m.mho/cm.^{2} for axon no. 21.

with which they are permitted to cross the membrane under this driving force. If this is in fact the case, we should expect that sodium ions would cross the membrane in both directions, the observed I_{Na} being the difference between the opposing currents carried by these two fluxes. At the sodium potential

the fluxes would be equal, making I_{Na} zero; as the membrane potential is increased from this value, the ratio of inward to outward flux would increase, making I_{Na} positive, and vice versa.

By making certain very general assumptions about the manner in which ions cross the membrane it is possible to derive an equation which predicts the effect of sodium concentration on sodium current. The theory on which this equation depends is closely connected with those of Behn (1897), Teorell (1949*b*) and Ussing (1949), but differs from them, both in the assumptions from which it is derived and in the range of cases to which it applies.

We assume only that the chance that any individual ion will cross the membrane in a specified interval of time is independent of the other ions which are present. The inward flux M_1 of any ion species will therefore be proportional to the concentration c_1 of that ion in the external fluid, and will not be affected by c_2, its concentration inside the axon. We may therefore write

$$M_1 = k_1 c_1, \tag{7}$$

where k_1 is a constant which depends on the condition of the membrane and on the potential difference across it. Similarly, the outward flux M_2 is given by

$$M_2 = k_2 c_2, \tag{8}$$

where k_2 is another constant, determined by the same factors as k_1 but in general different from it. Hence

$$M_1/M_2 = k_1 c_1/k_2 c_2. \tag{9}$$

The condition for equilibrium is that $M_1 = M_2$, so that

$$k_2/k_1 = c_1^*/c_2,$$

where c_1^* is the external concentration that would be in equilibrium with the (fixed) internal concentration, under the existing value of E, the membrane potential.

Substituting for k_1/k_2 in (9), we have

$$M_1/M_2 = c_1/c_1^*. \tag{10}$$

Now $c_1^*/c_2 = \exp(-EF/RT)$ and $c_1/c_2 = \exp(-E^*F/RT)$, where E^* is the equilibrium potential for the ion under discussion, so that

$$c_1/c_1^* = \exp(E - E^*)\, F/RT$$

and

$$M_1/M_2 = \exp(E - E^*)\, F/RT. \tag{11}$$

We now have in Equations (7), (8) and (11) three simple relations between M_1, M_2, c_1 and E. The effect of membrane potential on either of the fluxes alone is not specified by these equations, but is immaterial for our purpose.

If we wish to compare the sodium currents when the axon is immersed first in sea water, with sodium concentration $[Na]_o$, and then in a low-sodium

solution with sodium concentration $[Na]'_o$, the membrane potential having the same value E in both cases, we have:

$$\frac{I'_{Na}}{I_{Na}} = \frac{M'_{Na_1} - M'_{Na_2}}{M_{Na_1} - M_{Na_2}}.$$

From (7), $M'_{Na_1}/M_{Na_1} = [Na]'_o/[Na]_o$ and from (8) $M'_{Na_2} = M_{Na_2}$. Using these relations and Equation (11)

$$\frac{I'_{Na}}{I_{Na}} = \frac{([Na]'_o/[Na]_o)\exp(E - E_{Na})F/RT - 1}{\exp(E - E_{Na})F/RT - 1}. \tag{12}$$

Strictly, activities should have been used instead of concentrations throughout. In the final Equation (12), however, concentrations appear only in the ratio of the sodium concentrations in sea water and the sodium-deficient solution. The total ionic strength was the same in these two solutions, so that the ratio of activities should be very close to the ratio of concentrations. The activity coefficient in axoplasm may well be different, but this does not affect Equation (12).

Equation (11) is equivalent to the relation deduced by Ussing (1949) and is a special case of the more general equation derived by Behn (1897) and Teorell (1949*b*). All these authors start from the assumption that each ion moves under the influence of an electric field, a concentration gradient and a frictional resistance proportional to the velocity of the ion in the membrane. This derivation is more general than ours in the respect that it is still applicable if, for instance, a change in c_1 alters the form of the electric field in the membrane and therefore alters M_2; in this case, Equations (8) and therefore (12) are not obeyed. On the other hand, it is more restricted than our derivation in that it specifies the nature of the resistance to movement of the ions.

Agreement with experimental results. Equation (12) is tested against experimental results in Fig. 13. Section (*a*) shows data from the experiment illustrated in Figs. 3 and 6*a*. The values of the sodium current in sea water (I_{Na}) and in 30% Na sea water (I'_{Na}) were derived by the procedure described in the 'Results' section. The crosses are the peak values of I_{Na}, plotted against V, the displacement of membrane potential during the voltage clamp. A smooth curve has been fitted to them by eye. V_{Na} was taken as the position at which the axis of V was cut by this curve. Since

$$V = E - E_r, \quad (E - E_{Na}) = (V - V_{Na}),$$

and, for each point on the smoothed curve of I_{Na} against V, a corresponding value of I'_{Na} was calculated by means of Equation (12). These values are plotted as curve B. The experimentally determined peak values of I'_{Na} are shown as circles. These are seen to form a curve of shape similar to B, but of greater amplitude. They are well fitted by curve C, which was obtained from B by multiplying all ordinates by the factor 1·20.

Fig. 13*b*, *c* were obtained in the same way from experiments in which the low-sodium solutions were 10% Na sea water and choline sea water respectively. In each case, the peak values of I'_{Na} are well fitted by the values predicted by means of Equation (12), after multiplying by constant factors of 1·333 and 1·60 in (*b*) and (*c*) respectively.

These constant factors appear at first sight to indicate a disagreement with the theory, but they are explained quantitatively by an effect which is described in the fourth paper of this series (Hodgkin & Huxley, 1952*b*). The

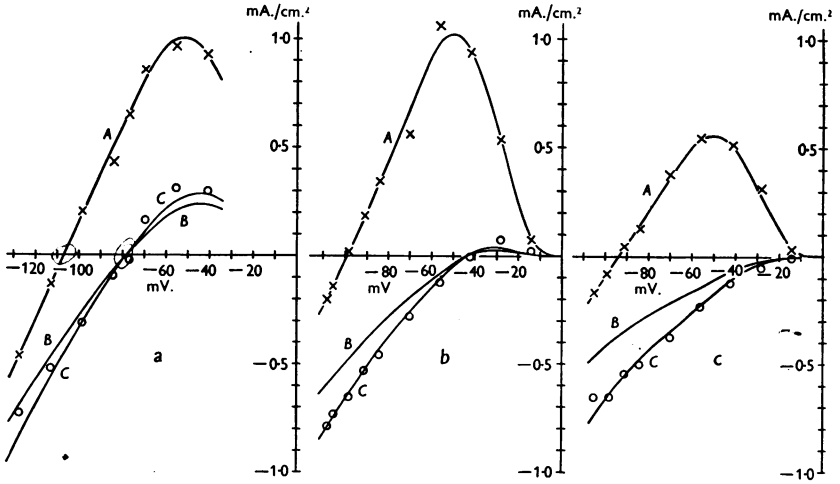

Fig. 13. Test of 'independence principle'. Three experiments. Crosses: peak sodium current density during voltage clamp; axon in sea water. Curve *A* fitted by eye. Circles: peak sodium current density during voltage clamp; axon in low sodium sea water. Curve *B*: peak sodium current density in low sodium sea water, predicted from curve *A* by Equation (12). Curve *C*: as curve *B*, but all ordinates multiplied by a factor *f*. Abscissa: membrane potential measured from resting potential in sea water. (*a*) Axon no. 20; temperature 6° C. Data from voltage clamps in (1) 30% sodium sea water, (2) sea water, (3) 30% sodium sea water. Circles are average values from runs (1) and (3). Value of V_{Na} inserted in Equation (12): −106·8 mV. Factor $f=1{\cdot}20$. (*b*) Axon no. 21; temperature 8·5° C. Data from voltage clamps in (1) 10% sodium sea water, (2) sea water, (3) 10% sodium sea water. Circles are average values from runs (1) and (3). $V_{Na}=-98{\cdot}8$ mV., $f=1{\cdot}333$. (*c*) Axon no. 21; temperature 8·5° C. Data from voltage clamps in (1) sea water, (2) choline sea water, (3) sea water, taken later than (*b*). Crosses are average values from runs (1) and (3). $V_{Na}=-93{\cdot}8$ mV., $f=1{\cdot}60$.

resting potential was higher in the low-sodium solutions than in sea water, and it is shown in that paper that increasing the membrane potential by current flow allows a subsequent depolarization to produce greater sodium currents than it would otherwise have done. The factor by which the sodium currents are thus increased is greater the lower the sodium concentration, and the poorer the condition of the fibre. The first of these effects explains why the factor is greater in (*b*) than in (*a*), while the second explains why it is greater in (*c*) than in (*b*). The experiments in Fig. 13*b*, *c* were performed on the same

fibre, and the deterioration between the experiments is shown by the fact that the I_{Na} values are only about half as great in (*c*) as in (*b*).

We can therefore say that, within experimental error, the sodium currents in sea water and in low-sodium solutions are connected by Equation (12), suggesting that the 'independence principle' from which this equation was derived is applicable to the manner in which the ions cross the membrane. This does not tell us much about the physical mechanism involved, since the 'independence' relations would be obeyed by several quite different systems. Examples are the 'constant field' system discussed by Goldman (1943), where the electric field through the membrane is assumed to be uniform and unaffected by the concentrations of ions present; and any system involving combination with carrier molecules in the membrane, so long as only a small proportion of the carrier is combined with the ion at any moment.

Origin of the action potential

The main conclusions that were drawn from the analysis presented in the 'Results' section of this paper may be summarized as follows. When the membrane potential is suddenly reduced (depolarization), the initial pulse of current through the capacity of the membrane is followed by large currents carried by ions (chiefly sodium and potassium), moving down their own electrochemical gradients. The current carried by sodium ions rises rapidly to a peak and then decays to a low value; that carried by potassium ions rises much more slowly along an S-shaped curve, reaching a plateau which is maintained with little change until the membrane potential is restored to its resting value.

These two components of the membrane current are enough to account qualitatively for the propagation of an action potential, the sequence of events at each point on the nerve fibre being as follows: (1) Current from a neighbouring active region depolarizes the membrane by spread along the cable structure of the fibre ('local circuits'). (2) As a result of this depolarization, sodium current is allowed to flow. Since the external sodium concentration is several times greater than the internal, this current is directed inwards and depolarizes the membrane still further, until the membrane potential reverses its sign and approaches the value at which sodium ions are in equilibrium. (3) As a delayed result of the depolarization, the potassium current increases and the ability of the membrane to pass sodium current decreases. Since the internal potassium concentration is greater than the external, the potassium current is directed outwards. When it exceeds the sodium current, it repolarizes the membrane, raising the membrane potential to the neighbourhood of the resting potential, at which potassium ions inside and outside the fibre are near to equilibrium.

The further changes which restore the membrane to a condition in which it

can propagate another impulse have also been studied by the 'voltage clamp' technique and are described in subsequent papers (Hodgkin & Huxley, 1952*a*, *b*). In the final paper of the series (Hodgkin & Huxley, 1952*c*), we show that an action potential can be predicted quantitatively from the voltage clamp results, by carrying through numerically the procedure which has just been outlined.

SUMMARY

1. The effect of sodium ions on the current through the membrane of the giant axon of *Loligo* was investigated by the 'voltage-clamp' method.

2. The initial phase of inward current, normally associated with depolarizations of 10–100 mV., was reversed in sign by replacing the sodium in the external medium with choline.

3. Provided that sodium ions were present in the external medium it was possible to find a critical potential above which the initial phase of ionic current was inward and below which it was outward. This potential was normally reached by a depolarization of 110 mV., and varied with external sodium concentration in the same way as the potential of a sodium electrode.

4. These results support the view that depolarization leads to a rapid increase in permeability which allows sodium ions to move in either direction through the membrane. These movements carry the initial phase of ionic current, which may be inward or outward, according to the difference between the sodium concentration and the electrical potential of the inside and outside of the fibre.

5. The delayed outward current associated with prolonged depolarization was little affected by replacing sodium ions with choline ions. Reasons are given for supposing that this component of the current is largely carried by potassium ions.

6. By making certain simple assumptions it is possible to resolve the total ionic current into sodium and potassium currents. The time course of the sodium or potassium permeability when the axon is held in the depolarized condition is found by using conductance as a measure of permeability.

7. It is shown that the sodium conductance rises rapidly to a maximum and then declines along an approximately exponential curve. The potassium conductance rises more slowly along an S-shaped curve and is maintained at a high level for long periods of time. The maximum sodium and potassium conductances were normally of the order of 30 m.mho/cm.^{2} at a depolarization of 100 mV.

8. The relation between sodium concentration and sodium current agrees with a theoretical equation based on the assumption that ions cross the membrane independently of one another.

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