ALAN LLOYD HODGKIN

The ionic basis of nervous conduction

Nobel Lecture, December 11, 1963

Trinity College, Cambridge, which I entered in 1932, has a long-standing connexion with neurophysiology. As an undergraduate I found myself interested in nerve and was soon reading books or papers by Keith Lucas[1], Adrian[2], Hill[3] and Rushton[4], all of whom are, or were, fellows of Trinity. I had a particular reason for looking at Lucas's papers-because my father and Lucas had been close friends and both lost their lives during the first world war: My reading introduced me to Bernstein's membrane theory[5], in the form developed by Lillie[6] and I thought it would be interesting to test their assumptions by a simple experiment. A central point in the theory is that propagation of the impulse from one point to the next is brought about by the electric currents which flow between resting and active regions. On this view, the action potential is not just an electrical sign of the impulse, but is the causal agent in propagation. Nowadays the point is accepted by everyone, but at that time it lacked experimental proof. By a roundabout route I came across a fairly simple way of testing the idea. The method depended on firing an impulse at a localised block, and observing the effect of the impulse on the excitability of the nerve just beyond the block. It turned out that the impulse produced a transient increase in excitability over a distance of several millimetres, and that the increase was almost certainly caused by electric currents spreading in a local circuit through the blocked region[7]. More striking evidence for the electrical theory was obtained later, for instance when it was shown that the velocity of the nerve impulse could be changed over a wide range by altering the electrical resistance of the external fluid*. But this is not the place to describe these experiments and I would like to take up the story again in 193 8, when I had the good fortune to spend a year in Gasser's laboratory at the Rockefeller Institute in New York. Before leaving Cambridge, I had found by a lucky accident that it was quite easy to isolate single nerve fibres from the shore crab, *Carcinus maenas.* This opened up several interesting lines and I became increasingly impressed with the advantages of working on single nerve fibres. *Carcinus* fibres are very robust, but they are at most 1/30 millimeter in diameter, and for many purposes this is inconveniently

small. There was a good deal to be said for switching to the very much larger nerve fibres which J. Z. Young[9] had discovered in the squid and which were then being studied by Curtis and Cole[10] in Woods Hole. Squids of the genus *Loligo,* are active creatures, one or two feet long, which can swim backwards at high speed by taking water into a large cavity and squirting out a jet through a funnel in the front of the animal. The giant nerve fibres, which may be as much as a millimeter in diameter, run in the body wall and supply the muscles that expel water from the mantle cavity. Although these fibres are unmyelinated, their large size makes them conduct rapidly and this may be the teleological reason for their existence. It should be said that large nerve fibres conduct faster than small ones[11] because the conductance per unit of the core increases as the square of the diameter whereas the electrical capacity of the surface increases only as the first power.

You may wonder how it is that we get along without giant nerve fibres. The answer is that vertebrates have developed myelinated axons in which the fibre is covered with a relatively thick insulating layer over most of its length, and the excitable membrane is exposed only at the nodes of Ranvier. In these fibres, conduction is saltatory and the impulse skips from one node to the next. I regret that shortage of time does not allow me to refer to this important development with which the names of Kato, Tasaki and Takeuchi[12] are particularly associated.

Early in 1938, K. S. Cole asked me to spend a few weeks in his laboratory at Woods Hole where squid are plentiful during the summer. I arrived in June 1938 and was greeted by a sensational experiment, the results of which were plainly visible on the screen of the cathode-ray tube. Cole and Curtis's had developed a technique which allowed them to measure changes in the electrical conductivity of the membrane during the impulse; when analysed, their experiment proved that the membrane undergoes a large increase in conductance which has roughly the same time course as the electrical change (Fig. 1). This was strong evidence for an increase in ionic permeability but the experiment naturally did not show what ions were involved, and this aspect was not cleared up until several years after the war. At first sight, Cole and Curtis's results seemed to fit in with the idea that the membrane broke down during activity, as Bernstein and Lillie had suggested. However, there was one further point which required checking. According to Bernstein, activity consisted of a momentary breakdown of the membrane, and on this view the action potential should not exceed the resting potential. Huxley and I started to test this point early in 1939. We measured external electrical changes from

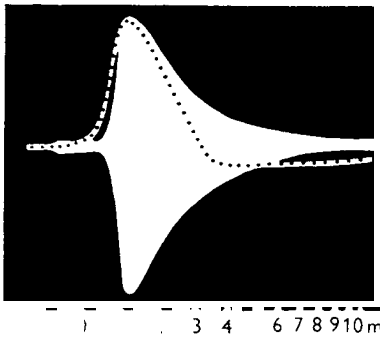


Fig. 1. Action potential (dotted curve) and increase in conductance (white band) in squid axon at about 6°C. From Cole and Curtis[13].

Carcinus fibres immersed in oil with a cathode ray tube, d. c. amplifier and cathode followers as the recording instrument. The resting potential was taken from the steady potential between an intact region and one depolarized by injury or by isotonic potassium chloride. To our surprise we found that the action potential was often much larger than the resting potential, for example 73 mV for the action potential as against 37 mV for the resting potential. (Although I was not aware of it until much later, Schaefer[14] had previously reported a similar discrepancy in the sartorius and gastrocnemius muscles of the frog.) Our results did not give the absolute value of the membrane potentials because of the short-circuiting effect of the film of sea water which clings to a fibre in oil. However, there is no reason why short-circuiting should affect one potential more than another and the discrepancy seemed much too large to be explained by some small difference in the way that the two potentials were recorded. Nevertheless we were extremely suspicious of these results with external electrodes, and before they could be published both of us were caught up in the war.

Before going further with the discrepancy, it seemed important to establish the absolute value of the membrane potentials by recording potential differences between an electrode inside the nerve fibre and the external solution. Osterhout and his colleagues[15] had recorded internal potentials by introducing electrodes into the vacuoles of large plant cells, but for obvious reasons the comparable experiment had not been attempted with nerve. The best preparation on which to try such an experiment was the giant axon of the squid, and the first measurements of this kind were made during the summer of 1939 by Curtis and Cole[16] at Woods Hole, and by Huxley and myself[17] at Ply-

mouth. There were minor differences in technique but the general principle was the same. A microelectrode consisting of a long glass capillary, filled with saline or metal, was inserted at one end of the fibre and pushed in for a distance of 10-30 mm. The fibre was damaged at the point where the capillary entered it, but an insertion of 10-30 mm was sufficient to take the electrode into intact nerve. During the insertion the electrode had to be kept away from the membrane; if it scraped against the surface, the axon was damaged. However, if kept clear of the membrane, the electrode did no harm, and it has since been shown that axons will conduct impulses for many hours after being impaled in this way. Fig. 2A shows an electrode inside an uncleaned axon; Fig. 2B is similar but the small nerve fibres round the giant axon have been removed and dark ground illumination has been used.

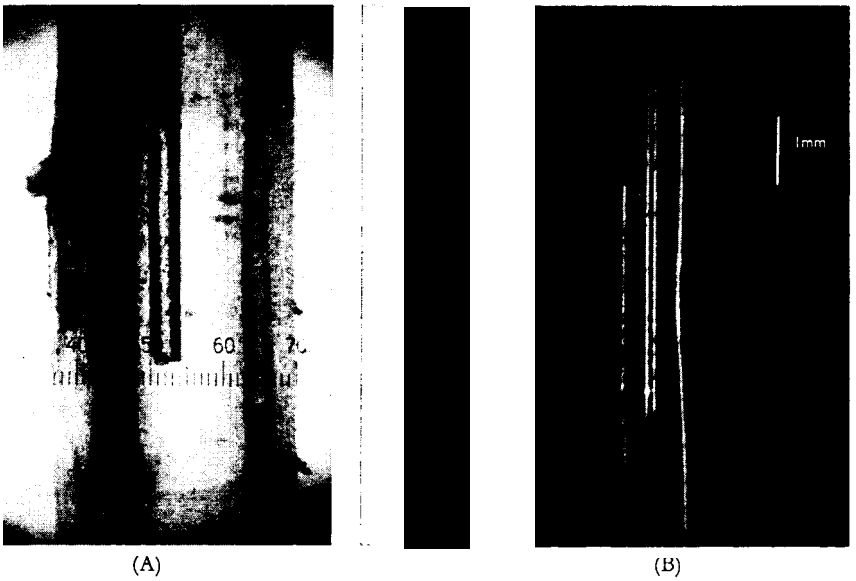


Fig. 2. (A) Photomicrograph of a recording electrode inside a giant axon of *Loligo forbesi.* The giant axon, which shows as a clear space was left with smallnerve fibres on either side; one division= 33 μ. From Hodgkin and Huxley[17]. (B) Cleaned giant axon of *Loligo forbesi* with glass tube 0.1 mm in diameter inside it; dark ground illumination. From Hodgkin and Keynes[20].

In 1939 both the Woods Hole and Plymouth groups found that large action potentials could be recorded between an internal electrode and the external solution, thus providing strong evidence for the idea that the action potential arises at the surface membrane. With this technique Huxley and I again obtained the disturbing result that the action potential was much greater than the

resting potential[17]. Fig. 3, which illustrates one of these experiments, shows an action potential of 86 mV and a resting potential of 45 mV. In their 1939 experiments Curtis and Cole[16] recorded the action potential with a condenser-coupled amplifier; later measurements[19] with a d. c. amplifier gave an average action potential of 108 mV and an average resting potential of 51 mV. Curtis and Cole also showed that the resting potential could be abolished, reversibly, by increasing the external potassium concentration until it was about the same as that in the axoplasm; at high concentrations the membrane behaved like a potassium electrode, as predicted by Bernstein's theory.

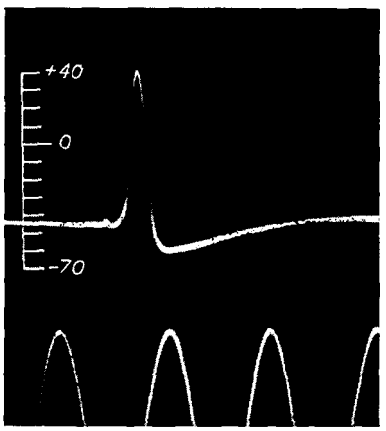


Fig. 3. Action potential and resting potential recorded between inside and outside of axon with capillary filled with sea water. Time marker 500 cycles/set. The vertical scale indicates the potential of the internal electrode in millivolts, the sea water outside being taken as at zero potential. From Hodgkin and Huxley[17] see also ref. 18.

The small size of most nerve or muscle fibres made it difficult to extend the technique employed for the giant axon to other preparations. However, another very convenient and powerful method was developed by Graham, Gerard and Ling, who showed that extremely small glass capillaries could be inserted transversely into muscle fibres without causing appreciable damage[21]. In order to obtain consistent results it is desirable that the electrodes should have an external diameter of less than 0.5 μ. This small diameter means that the electrodes have a high resistance and special precautions must be taken with the recording system. Initially the electrodes were used to measure the resting potential, but increasing the concentration of the KC1 in the electrode to 3 *M* enabled the action potential to be recorded as well[22]. Many types of

excitable cell have been now examined and in nearly every case it has been found that the action potential exceeds the resting potential, often by 40 or 50 mV.

Yet another method is required for myelinated nerve fibres, which do not take kindly to impalement. A useful way of eliminating external short circuiting was introduced by Huxley and Stämpfli[23] in 1950 and their method has been refined in a very elegant way by Frankenhaeuser[24]. The values found by applying these methods of amphibian nerve fibres are: action potential 120 mV and resting potential 70 mV. Absolute values for mammalian nerve fibres are unknown, but they are probably not very different from those reported for frog.

At the end of the war, the position was that several of Bernstein's assumptions had been vindicated in a striking way, but that in one major respect the classical theory had been shown to be wrong. By 1945 most neurophysiologists agreed that the action potential was propagated by electric currents, and that it arose at the surface membrane; it was also clear that the resting potential was at least partly due to the E. M. F. of the potassium concentration cell. On the other hand, there was impressive evidence that in both crab and squid fibres the action potential exceeded[17-19] the resting potential by 40-50 mV. This was obviously incompatible with the idea that electrical activity depended on a breakdown of the membrane; some process giving a reversal of E. M. F. was required.

sodium hypothesis

There were several early attempts to provide a theoreticalbasis for the reversal, but most of these were speculative and not easily subject to experimental test. A simpler explanation, now known as the sodium hypothesis, was worked out with Katz and Huxley[25], and tested during the summer of 1947. The hypothesis, which owed a good deal to the classical experiments of Overton[26], was based on a comparison of the ionic composition of the axoplasm of squid nerve with that of blood or sea water. As in Bernstein's theory, it was assumed that the resting membrane is selectively permeable to potassium ions and that the potential across it arises from the tendency of these ions to move outward from the more concentrated solution inside a nerve or muscle fibre. In the limiting case, where a membrane which is permeable only to potassium separates axoplasm containing 400 m*M* K from plasma containing 20 m*M* K, the

internal potential should be 75 mV negative to the external solution. This value is obtained from the Nernst relation

$$V_K = \frac{RT}{F} \ln \frac{[K]_o}{[K]_i}$$

where V_K is the equilibrium potential of the potassium ion defined in the sense internal potential minus external potential, $[K]_o$ and $[K]_i$ are potassium concentrations (strictly activities) inside and outside the fibre. Resting potentials of 70 mV have been observed in undissected squid axons[27]; the smaller values found in isolated axons may be explained by a leakage of sodium into the fibre. If the permeability to sodium were 1/12 that to potassium, a potential of about 50 mV is predicted for an isolatedaxon in sea water (350 m*M* K, 50 m*M* Na in axoplasm, 10 m*M* K, 450 m*M* Na in sea water).

From Bernstein's theory it might be assumed that when the membrane broke down, the ratio of the permeabilities to Na and K would approach that of the aqueous mobilities of these ions, about 0.7 to 1. In that case, the action potential could not exceed the resting potential and would in fact be less by at least 8 mV. However, it is simple to rescue the hypothesis by assuming that the active membrane undergoes a large and selective increase in the permeability to sodium. In the extreme case, where the membrane is much more permeable to sodium than to any other ion, the potential should approach that given by the Nernst formula, *i.e.*

$$V_{Na} = \frac{RT}{F} \ln \frac{[Na}{[Na} \qquad (2)$$

This gives a limiting value of + 58 mV for the 10-fold concentration ratio observed by Steinbach and Spiegelman[28] and accounts satisfactorily for the reversal of 50 mV commonly seen in intact axons.

A simple consequence of the sodium hypothesis is that the magnitude of the action potential should be greatly influenced by the concentration of sodium ions in the external fluid. For the active membrane should no longer be capable of giving a reversed E. M. F. if the concentration of sodium is equalised on the two sides of the membrane. The first quantitative tests were made with Katz- in the summer of 1947. They showed that the action potential, but not the resting potential, was reduced by replacing external sodium chloride with -choline chloride or with glucose. If all the external sodium was removed the axon became reversibly inexcitable, in agreement with Overton's experiment on frog muscle. Fig. 4 illustrates one of the experiments. In the physiological

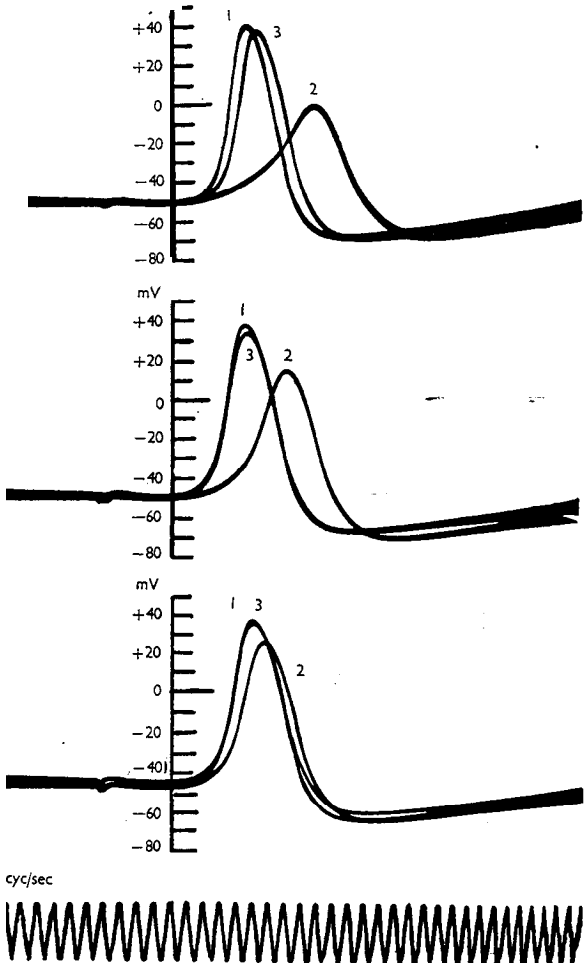


Fig. 4. Effect of sodium-deficient external solutions on the action potential of a giant axon. Records labelled 1 and 3 were with the axon in sea water; A2 with 0.3 3 sea water 0.67 isotonic dextrose; B2 with 0.5 sea water 0.5 isotonic dextrose; C2 with 0.7 sea water 0.3 isotonic dextrose. From Hodgkin and Katz[25].

region, the overshoot varied with externalsodium concentrations in the same manner as a sodium electrodeas.

It was also shown that a solution containing extra sodium increased the overshoot by about the amount predicted by eqn.2. This is a particularly satisfactoryresult, because it seems most unlikely that an increase beyond the normal could be brought about by an abnormal solution. Fig. 5 illustrates one of these experiments. Later, Stämpfli[29] showed that at the node of Ran-

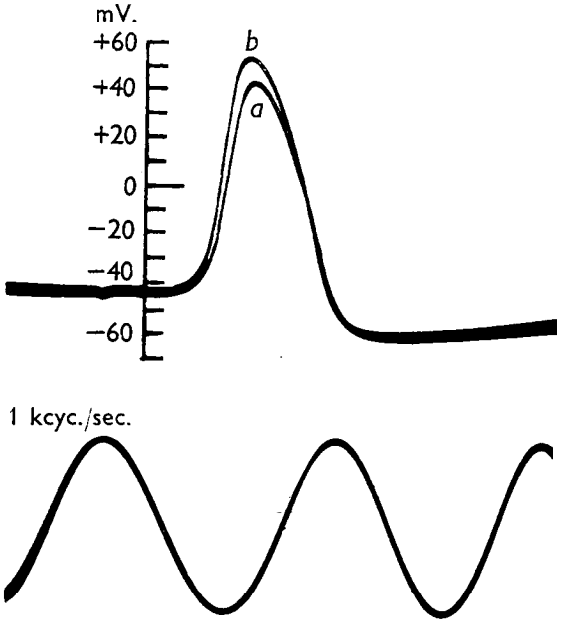


Fig. 5. Effect of sodium-rich external solution on the action potential of a giant axon. Record a in sea water; record b, 50 sec after applying sea water containing additional NaCl (Na concentration 1.56 times that in sea water). From Hodgkin and Katz[25].

vier an increase of about 35 mV in the overshoot is brought about by a four-fold increase of external sodium.

The effect of varying external sodium concentration has now been studied on a number of excitable tissues: for example frog muscle[22], myelinated nerve[30], Purkinje fibres of the heart[31] and crustacean nerve[32]. In all these cases the results were very similar to those in the squid axon.

There are at least two cases where the mechanism is thought to be basically different. These are crab muscle in which an entry ofcalcium, or other divalent cations, provides the inward current[33], and the plant cell *Chara* where an exit of chloride ions from the vacuolar sap may be the primary process[34].

Ionic movement during actii

During the period 1947-51 several investigators started to measure the effect of stimulation on the movements of labelled sodium across the surface membrane of giant axons. As often happens, work proceeded independently and

more or less simultaneously on the two sides of the Atlantic, the principal investigators being Keynes[35] in England and Rothenberg[36], Grundfest and Nachmansohn[37] in America. In 1949 Keynes reported that stimulation of Sepia axons at 100/sec caused a 15-fold increase in the rate of uptake of ^{24}Na. There was also a substantial increase in the outflow of labelled sodium and at first it was difficult to decide whether activity was associated with a net uptake of sodium. Keynes and Lewis[38] resolved the difficulty by measuring the sodium concentration in axoplasm by activation analysis, and there is now general agreement that at 20ºC the net entry of sodium in one impulse amounts to $3\text{-}4 \cdot 10^{-12}$ mole per square centimetre. Other experiments showed that a similar quantity of potassium ions leave the fibre during an impulse[39]. It is perhaps easier to get an idea of what these quantities mean by saying that one impulse is associated with an inward movement of 20 000 sodium ions through one square micron ofsurface.

An entry of $4 \cdot 10^{-12}$ moles of sodium per square centimetre is more than enough to account for the action potential. From the work of Cole and his colleagues it is known that the electrical capacity of the membrane is about one microfarad per square centimetre[10]. The quantity of charge required to change the voltage across a one microfarad condenser by 120 mV is $1.2 \cdot 10^{-7}$C; this is equivalent to $1.2 \cdot 10^{-12}$ mole of monovalent cation which is only one- third of the observed entry of sodium. A discrepancy in this direction is to be expected. In addition to charging the membrane capacity during the rising phase of the action potential, a good deal of Na exchanges with K, particularly during the early part of the falling phase. From the quantitative theory which Huxley and I developed, the size of the ionic movements can be predicted from electrical measurements. As Huxley will describe, the theoretical quantities turn out to be in reasonable agreement with experimental values.

The quantity of sodium which enters a myelinated axon during an impulse is much less than in an unmyelinated fibre of comparable size[40]. This is presumably because the ionic exchange is confined to the node of Ranvier and the capacity per unit length of the axon is reduced by the thick myelin sheath.

lysis of membrane currents: voltage clamp experiments

In pursuing the evidence for the ionic theory I have departed from the strict order of events. During the summer of 1947 Cole and Marmont[41,42] developed a technique for impaling squid axons with long metallic electrodes;

with the aid of electronic feedback they were then able to apply current uniformly to the membrane and to avoid the complications introduced by spread of current in a cable-like structure. Cole[41] also carried out an important type of experiment, again using feedback, in which the potential difference across the membrane is made to undergo a step-like change and the experimental variable is the current which flows through the membrane. In Cole's experiments a single internal electrode was used for recording potential and passing current; since the current may be large, electrode polarization introduces an error and makes it difficult to use steps longer than a millisecond. However, the essential features of the experiment, notably the existence of a phase of inward current over a range of depolarizations, are plainly shown in the records, which Cole[41] obtained in 1947. It was obvious that the method could be improved by inserting two internal electrodes, one for current, the other for voltage, and by employing a feedback amplifier to supply the current needed to maintain a constant voltage. Cole, Marmont and I discussed this possibility in the spring of 1948 and it was used at Plymouth the following summer by Huxley, Katz and myself[43]. Further improvements were made during the winter and in 1949 we obtained a large number of records which were analysed in Cambridge during the next two years[44]. Huxley will describe these results in more detail; here all that need be said is that by varying the external ionic concentrations it was possible to separate the ionic current flowing through the membrane into components carried by sodium and potassium, and hence to determine how the ionic permeability varied with time and with membrane potential.

To begin with we hoped that the analysis might lead to a definite molecular model of the membrane. However, it gradually became clear that different mechanisms could lead to similar equations and that no real progress at the molecular level could be made until much more was known about the chemistry and fine structure of the membrane. On the other hand, the equations that we developed proved surprisingly powerful and it was possible to predict much of the electrical behaviour of the giant axon with fair accuracy. Examples of some of the properties of the axon which are fitted by the equations are: the form, duration and amplitude of the action potential; the conduction velocity; impedance changes; ionic movements; and subthreshold phenomena including oscillatory behaviour.

Experimental work on giant axons since 1952: active transport of Na and K

In the last part of this lecture I should like to mention some of the more recent developments in the ionic theory of nervous conduction. One major problem, which has interested a number of physiologists and biochemists, is to find out how cells use metabolic energy to move sodium and potassium ions against concentration gradients. In excitable tissues this process is of particular interest because it builds up the ionic concentration differences on which conduction of impulses depends. When a nerve fibre carries an impulse it undergoes a rapid cycle of permeability changes which allow first sodium and then potassium ions to move down concentration gradients. In giant axons, the changes associated with an impulse are exceedingly Call, as can be seen from the fact that a 500y axon loses only one millionth of its internal potassium in a single impulse. Large fibres can therefore conduct many impulses without recharging their batteries by metabolism. Nevertheless, if they are to be of any use to the animal, nerve fibres must be equipped with a mechanism for reversing the ionic exchanges that occur during electrical activity. The necessity for such a system was foreseen by Overton in 1902 when he pointed out that human heart muscle carried out some $2.4 \cdot 10^9$ contractions in 70 years, yet as far as he knew contained as much potassium and as little sodium in old age as in early youth[26]. Forty years later Dean introduced the idea of a sodium pump and showed that the distribution of potassium and chloride in muscle might be a passive consequence of an active extrusion of sodium, but that active transport of potassium or chloride ions would by themselves be inadequate[45]. The concept was developed further by Krogh[46] and Ussing[47] and is now supported by experiments on a wide range of animal tissues.

Giant nerve fibres provide excellent material for studying ion pumping. One approach is to inject radioactive sodium ions and to collect the labelled ions which emerge from the fibre. Such experiments show that if the fibre is poisoned with cyanide or dinitrophenol it stops pumping, and sodium ions gradually accumulate inside. The fibre remains excitable for many hours because sodium and potassium can still move downhill during the impulse. But any sodium which gets into the fibre remains there and is not extruded as it would be in an unpoisoned axon. The ability to extrude sodium depends on the presence of ATP, and with an axon in which all the ATP has been broken down, sodium extrusion can be restored by injecting energy-rich phosphate in the right form[48]. Fig. 6 illustrates one of these experiments. It shows that the outflow of sodium is reduced to a low value by cyanide and can be restored

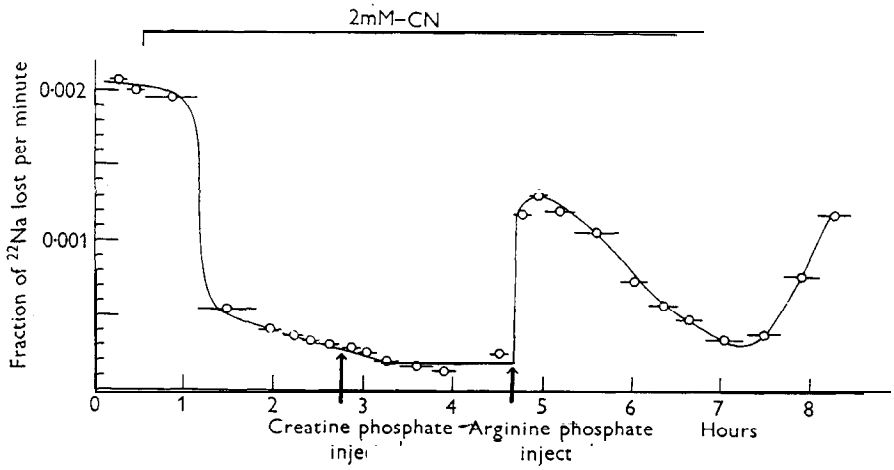


Fig. 6. Effect on outflow of sodium of (I) poisoning with cyanide, (2) injecting creatine phosphate, (3) arginine phosphate, (4) removal of cyanide. The mean concentrations in the axon after injection were 15.3 m *M* creatine phosphate and 15.8 m*M* arginine phosphate. From Caldwell *et al.* [48].

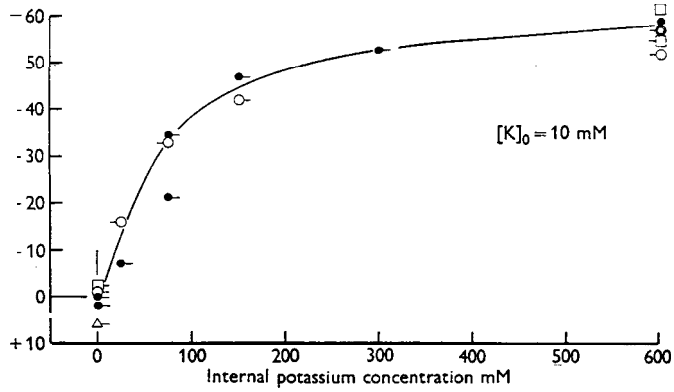
by the molluscan phosphagen, arginine phosphate, but not by the vertebrate phosphagen, creatine phosphate. This is a satisfactory result since it is known that creatine phosphate is not handled by the enzyme which catalyses the transfer of phosphate from arginine phosphate to ADPN.

The molecular nature of the pumping mechanism is unknown but there is much evidence to show that in most cells it is driven by compounds containing energy-rich phosphate, such as ATP or phosphagen. Recent interest in this field has been focussed by Skou on an ATP-splitting enzyme which is present in the membrane and has the interesting properties of being activated by sodium and potassium and inhibited by substances which interfere with sodium transport[50].

Perfusion of giant axons

In conclusion I should like to mention an interesting new method which has been developed during the last few years. Since the action potential of a nerve fibre arises at the surface membrane it should be possible to replace the protoplasm inside the fibre with an aqueous solution of appropriate composition. Methods for perfusing axons were worked out by Tasaki and his colleagues at Woods Hole[51] and by Baker and Shaw at Plymouth[52]. The technique used

at Plymouth is based on the observation[53] that most of the axoplasm in giant nerve fibres can be squeezed out of the cut end. This has been known since 1937 but until fairly recently no one paid much attention to the electrical properties of the thin sheath which remained after the contents of the nerve fibre had been removed. Since extrusion involves flattening the axon with a glass rod or roller it was natural to suppose that the membrane would be badly damaged by such a drastic method. However in the autumn of 1960 Baker and Shaw[52] recorded action potentials fromextruded sheaths which had been refilled with isotonic solution of a potassium salt. On further investigations[54] it turned out that such preparations gave action potentials of the usual magnitude for several hours, and that these were abolished, reversibly, by replacing K with Na in the internal solution. As can be seen from Figs. 7 and 8 the resting potential and action potential vary with the internal concentrations of K and Na in a manner which is consistent with the external effect of these ions.



7. Effect of varying internal potassium concentration on the resting potential. External solution, sea water containing 10 m*M* K; internal solution NaCl-KC1 solutions isotonic with sea water. Note that the resting potential reaches a limiting value of about - 55 mV at potassium concentration greater than 150 m*M*. From Baker *et al.* [54].

A point of some general interest is that although about 95% of the axoplasm had been removed, axon membranes perfused with isotonic potassium solutions were able to carry some 300 000 impulses. This reinforces the idea that chemical reactions in the bulk of the axoplasm are not essential for conduction of impulses and that ionic concentration gradients provide the immediate source of energy for the action potential. Huxley will tell you more about the way in which this is done.

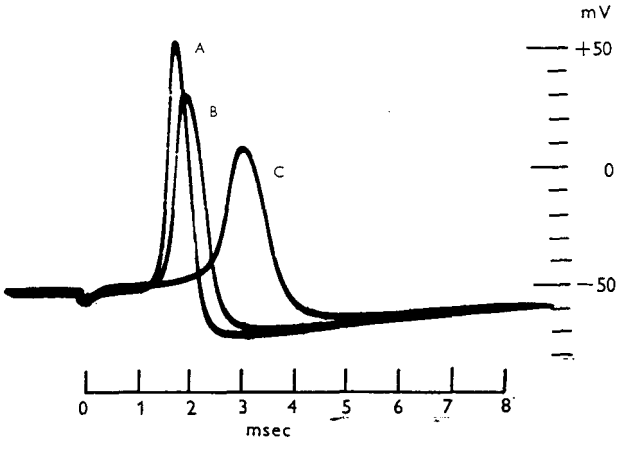


Fig. 8. Effect on action potential of replacing internal potassium with sodium ions. (A) isotonic potassium sulphate; (B) 0.25 K replaced by Na. (C) 0.5 K replaced by Na. The records were obtained in the order B, A, C. From Baker *et al.* [54].

Acknowledgements

From the bibliography which is far from complete) it is evident that the development of the ionic theory has been very much a cooperative effort and I wish to thank all those who have contributed to it. For more direct help, my particular thanks are due to W. A. H. Rushton, K. S. Cole, H.J. Curtis, A. F. Huxley, B. Katz and R. D. Keynes.

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