THE EFFECT OF ORGANIC IONS ON THE MEMBRANE POTENTIAL OF NERVES

By W. WILBRANDT*

(From the Department of Physiology, School of Medicine, University of Pennsylvania, Philadelphia, and the Marine Biological Laboratory, Woods Hole)

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The phenomenon of the injury potential of nerve and muscle is generally explained by the assumption of a membrane surrounding the individual cell and separating two different electrolyte solutions inside and outside of the cell. The potential, then, is due to the particular properties of the membrane, and to the fact that the ionic composition of the cell content differs widely from that of the intercellular fluid.

As to the first point, different views are held. (1) The membrane acts as a molecular sieve (Ostwald (1890), Bernstein (1902), Höber (1905), Michaelis (1926), Netter (1928)) and the potential is essentially a diffusion potential. (2) The membrane is a homogeneous non-aqueous layer and the potential is a phase boundary potential (Beutner (1920)). (3) The membrane is a homogeneous non-aqueous layer and the potential is a diffusion potential (Osterhout (1933)).

The purpose of the present paper is not primarily to furnish evidence for one of these views. Part of its results are, however, best understood, as will be shown, by the assumption of a porous structure. Also for reasons discussed in another paper we prefer the first interpretation, assuming that an oriented molecular structure rather than a homogeneous phase constitutes the membrane. Investigations on x-ray patterns of nerves, in which definite interferences could be attributed to the myelin sheath (Boehm (1933)), seem to justify this assumption, at least for the myelin sheath.

As to the second point, several workers have shown that the ionic content of the nerve fibers is very different from the intercellular

* Fellow of The Rockefeller Foundation.

fluid, especially with respect to potassium. Since this ion has a particular effect on the injury potential of muscle and nerve the assumption was made that the potential is mainly due to the unequal distribution of potassium.

Recent work, however, seems to indicate that this view is incomplete. A connection between metabolism and nerve potential was suggested by the work of Gerard (1929) and Furusawa (1930), who found a reversible decrease of the injury potential in absence of oxygen. Also the after potentials during activity seem to be connected with the metabolism of the nerve (Levin (1927), Gerard (1929), Amberson and Downing (1929–30), Furusawa (1930), Gerard (1930), Amberson, Parpart, and Sanders (1931)). It may be argued that the membrane itself is injured by the asphyxia, losing temporarily its characteristic properties; in terms of the theory of Bernstein and Höber, its selective cation permeability or its selective potassium permeability. It is, however, hard to explain how the effect can be reversible, since no force seems to be present to drive back the potassium which left the cell during the time of increased permeability.

Some dynamic factor, related to the metabolic activity of the cell, seems to be lacking in the present picture of the potential mechanism. A different kind of connection may be suggested, therefore. The metabolism furnishes ionized metabolites which, without necessarily affecting the membrane, act on the potential. The recent excellent work of Teorell may be mentioned here. He has worked out both theoretically and experimentally a more general type of Donnan equilibrium, in which a constant diffusion gradient of diffusing ions (diffusion agent) keeps up an unequal distribution of originally equally distributed ions (passive ions), the potential being related to the distribution of passive ions in the same logarithmic way as in the original Donnan equilibrium. It seems possible that in some similar way the continuous metabolism of the nerve cell is, by means of diffusing ionized metabolites, related to the nerve membrane potential.

We know the reversible influence of inorganic ions on the potential. To judge the probability of a relation as discussed above, it seems first of all necessary to know whether organic ions can exert a similar reversible influence, and if so, whether relations between such an

influence and the physical properties of the ions in question can be found.

The present paper deals mainly with this question. It shows a distinct, and to a certain degree reversible, influence of organic ions on the nerve injury potential, and, for the homologous series of the dialkylamines, a relation of the efficacy of an ion to its position in the series. The interpretation of this relation will be discussed.

Furthermore the results obtained on myelinated nerves are compared to those on non-myelinated nerves, to test, in how far they are due to the specific nature of the myelin sheath and in how far to a nerve membrane, common to all types of nerves.

Method

The nerves used were the sciatic nerve of *Rana pipiens* and the non-myelinated limb nerve (mostly of the first and second leg, sometimes of the claw) of the spider crab, *Maia squinado*. They were carefully prepared and usually immersed in oxygenated Ringer or sea water for about $^1/_2$ or 1 hour before the experiment.

The active lead was made in Ringer or sea water, the inactive, instead of using a cut, in isotonic KCl solution. This yields a potential of 20–40 mv., which does not decrease due to recovery as in the case of a cut nerve. The slow fall of the potential which still takes place is due to a decrease of the potential at the active (Ringer or sea water) lead. With good frog nerves it was sometimes only a few millivolts in 24 hours, with crab nerves more.

A chamber of paraffin wax was used as shown in Fig. 1. The nerve was drawn through four compartments, connected by hollow glass beads at the bottom. Two were filled with purest mercury (redistilled, for use with electrodes) and served as seals. (Control experiments with vaseline seals showed that the presence of mercury does not affect the potential during 24 hours.) Of the other two, which could be filled with solutions by means of an inlet and outlet, one contained isotonic KCl solution, the other Ringer (for frog nerves) or sea water (for crab nerves).

Leads were made through the inlets as shown in Fig. 1C. By means of agar bridges the calomel half cells could be connected successively with several chambers, so that several nerves could be used simultaneously. The calomel half cells were connected to a Leeds and Northrup student potentiometer and readings made with a box galvanometer (No. 2420) of Leeds and Northrup, whose sensitivity was 1.3×10^{-8} amp./mm. scale, after focussing the image of the galvanometer out of the box on a scale at about 3/4 meter distance.

To test the effect of a salt, the Ringers solution (or sea water) was replaced by an isotonic solution of the salt, mixed with Ringer (or sea water) in a ratio

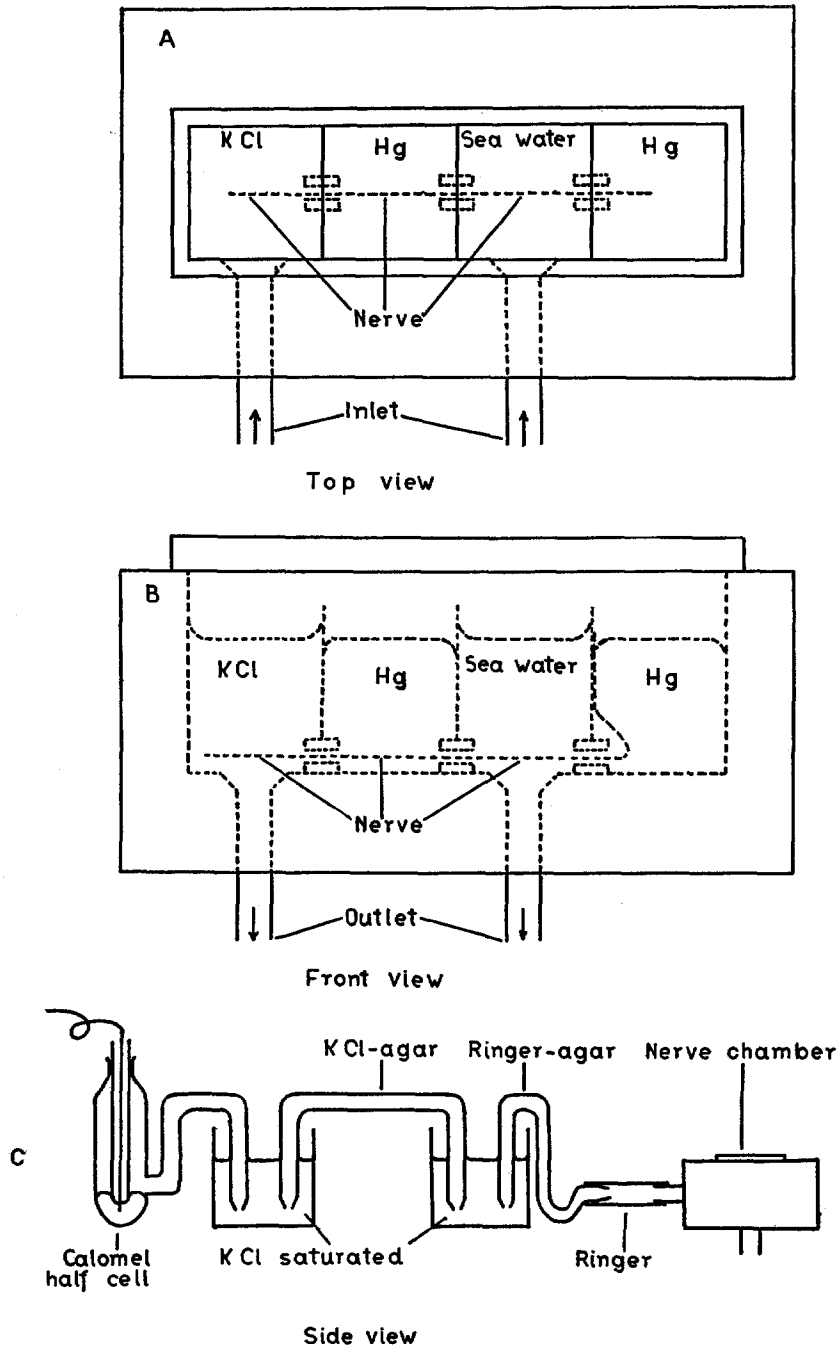

FIG. 1. Chamber of paraffin wax used in the experiments

varied according to the activity of the salt. 1/10 KCl in the records means, for instance, that Ringer was replaced by a mixture of 1/10 isotonic KCl and 9/10 Ringer. The salt solutions were neutralized, to a pH of 7–7.5, when applied in Ringer, and about 8, when applied in sea water. The Ringer solution was buffered with phosphate. Fresh filtered sea water was used. After a certain time, pure Ringer or sea water was introduced again to test the reversibility of the effect. In the case of frog nerves, this time was about 1 hour, in the case of crab nerves about 10–15 minutes. Diffusion in frog nerves is very slow, due to the great amount of connective tissue around the nerve and between the fibers, whereas the crab nerves have little connective tissue and the nerves split into fine bundles as soon as they are immersed in sea water. Thus in the latter the nerve fibers are reached by the electrolyte much faster than in frog nerves. By splitting the connective tissue of frog nerves under the microscope with a quartz needle the diffusion time could be shortened considerably. The nerves seemed, however, to be damaged by the procedure and it was not used in the experiments.

The salts used were the purest available preparations of Merck and Eastman Kodak. They were not further purified.

Since the nerves showed considerable individual variations as to their response to ions, several electrolytes were always tested on the same nerve and, especially between ions of about equal efficacy, comparisons were made only on the same nerve. Even then, however, the comparison was sometimes difficult due to the fact that the response of a nerve decreases with time.

Effect of Inorganic Ions on the Potential of the Non-Myelinated Nerve of the Spider Crab

Netter has investigated the effect of inorganic ions on the membrane potential of the sciatic nerve of the frog (Netter (1928)). He found that cations only affected the potential, the effect decreasing in the series Li = Na < Cs < NH_4 < Rb < K. Anions had no effect. He concluded that the nerve membrane is solely cation permeable and consists of a pore system since the series he found was about that of the ionic sizes.

As far as cations are concerned, the results in crab nerves agree fairly well with Netter's, as Fig. 2 shows. Rb and K lower the potential in very high dilution, (1/40 was still found to be effective), Rb slightly more than K (Fig. 2A). NaCl in high concentrations (1/4 – 3/4 was mostly used) raises the potential a few millivolts (Fig. 2B). This is due to the dilution of the highly active K, as could be shown in experiments with artificial sea water, in which a corresponding lowering of the K concentration yielded the same result. Li

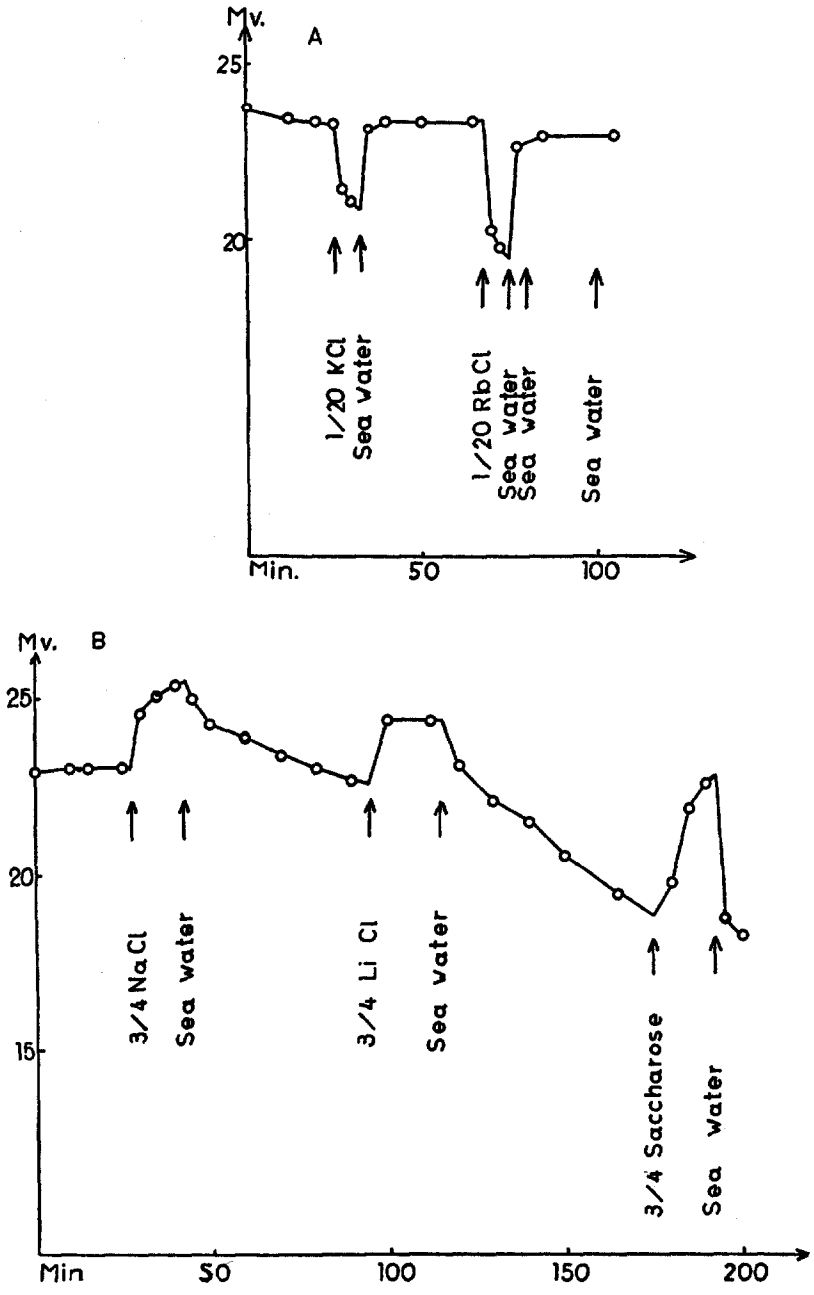

FIG. 2. Effect of inorganic cations on the potential of crab nerves

has about the same effect as Na (Fig. 2B). Both, however, although much less active than K and Rb, do also have a slight lowering influence on the potential. This is shown when instead of NaCl or LiCl an isotonic solution of a non-electrolyte (saccharose) equally diluted with sea water is applied. Then, with equal dilution of the potassium, the potential rises considerably higher (Fig. 2B), which shows the lowering effect of Na and Li.

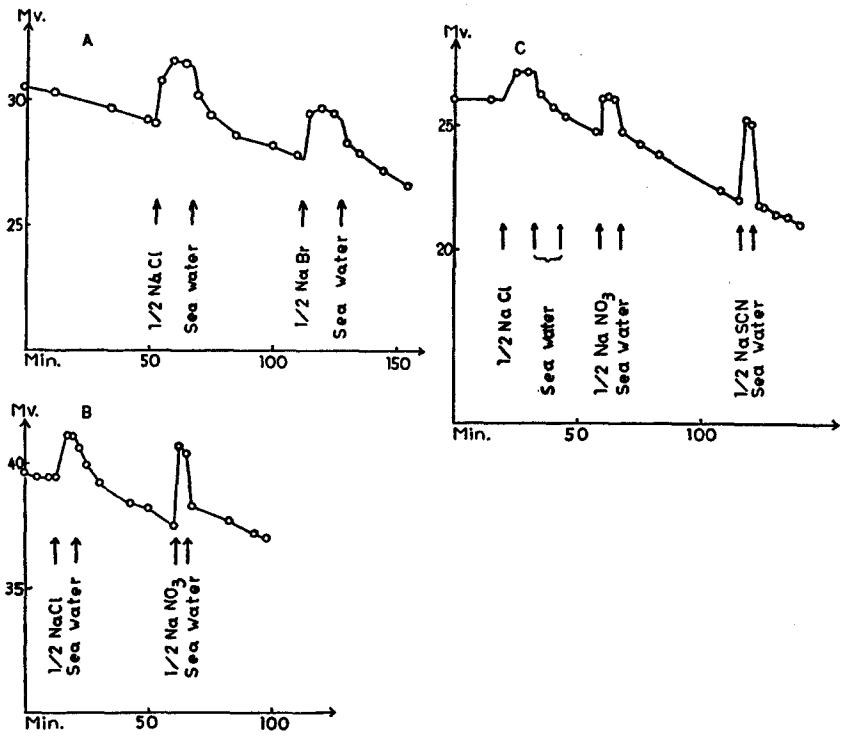

FIG. 3. Effect of inorganic anions on the potential of crab nerves

The cations thus act in the series Rb > K > Na = Li, which agrees with Netter's results except the position of Rb.

Anions, however, in contrast to Netter's results, were found to have a distinct, if slight, effect on the potential. Since they have the opposite sign their effect, if they are active, must of course be to raise the potential. NaBr, $NaNO_3$, and NaSCN were used. The dilution

of the potassium was taken into account by comparing the effect in each case with that of NaCl in the same concentration. Fig. 3 shows, that, whereas NaCl and NaBr have about the same effect, $NaNO_3$ and, more definitely, NaSCN, raise the potential higher than NaCl does.

Since the effect was only a few millivolts the possible interference of diffusion potentials was checked. A silk thread was used instead of the nerve in the same arrangement, and the effect of the salts tested in the same concentrations as on the nerve. The potential did not change by more than 3/10 mv. In the presence of 1/2 sea water diffusion potentials are depressed considerably.

The series of activity of the anions is:

$Cl = Br \leqq NO_3 < SCN$. Their efficacy is about comparable to that of Li and Na, but much lower than that of K and Rb. The assumption of a completely anion impermeable membrane, therefore, cannot be made for the non-myelinated nerve. Whether it is strictly true for the myelinated nerve should be tested again. The very slow diffusion in the latter, together with the slightly injurious effect of SCN, might conceal a slight rise of the potential. It may be noted, that in Netter's paper evidence against the assumption of complete anion impermeability can be found. He found that the concentration effect of K was considerably higher than that of Na and Li, which is not possible for an exclusively cation permeable membrane for thermodynamic reasons. Accordingly collodion membranes with high concentration effect, *i.e.* nearly exclusive cation permeability, were shown to have the same concentration effect for all cations (Michaelis (1926)). The concentration effect on nerves is, of course, lowered by the intercellular short circuit, but this effect should be about the same for all cations.

The Effect of Organic Ions on the Potential of Frog Nerves and Crab Nerves

A. Cations.—To avoid complications by hydrolysis only salts of strong bases were chosen: dialkylamines, tetraalkylamines, guanidine, and choline.

Fig. 4 shows the effect of dialkylamines (from dimethylamine to diamylamine) on the potential of crab nerves. Under the influence of the lower members in high concentration, from dimethylamine to

dipropylamine, the potential changes very little, which means taking into account the dilution of potassium (*cf.* Fig. 2B), that their lowering effect is weak, but a little stronger than that of Na. The effect decreases slightly from dimethylamine to dipropylamine. From the next member on, dibutylamine, the tendency is reversed. Dibutyl-

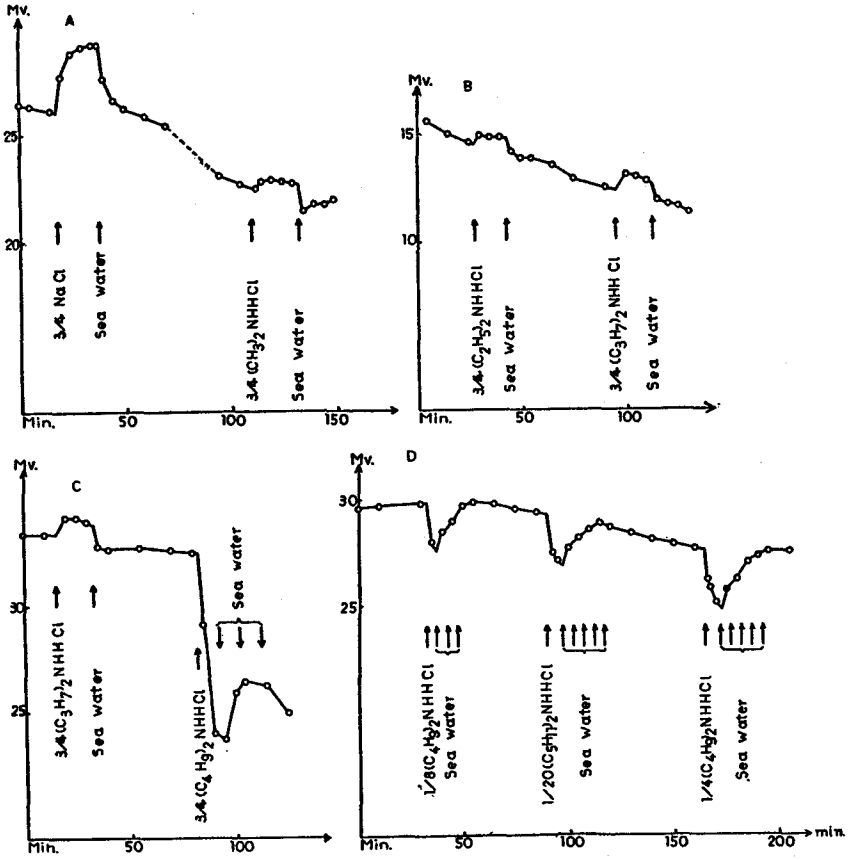

FIG. 4. Effect of dialkylamines on the potential of crab nerves

amine has a strong effect, with the concentration 3/4 the potential falls in a few minutes by 10 mv. but the fall is not completely reversible (Fig. 4C). In a lower concentration, 1/8, a reversible effect can be obtained (Fig. 4D). Diamylamine is still more active, even 1/20 lowers the potential rapidly and considerably, the efficacy being about

the same as that of K. In higher concentrations the reversibility is incomplete for this salt, too. This is a common feature of the active organic ions.

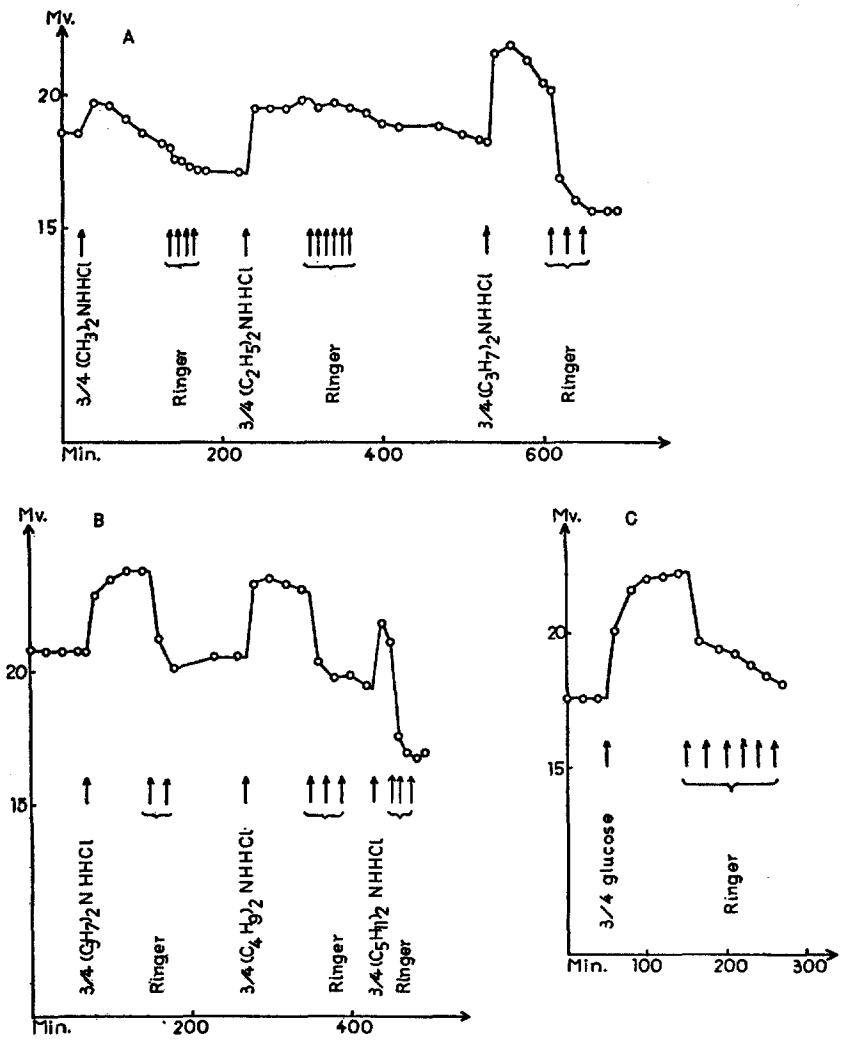

FIG. 5. Effect of dialkylamines on the potential of the frog sciatic nerve

Thus, ascending in the homologous series, there appears a decrease first, and then an increase in the effect on the potential. The same is

true for the effect of the same salts on the potential of frog nerves, but the reversing point is different, dibutylamine is still inactive, only diamylamine shows a strong effect. This is shown in Fig. 5. Dipropylamine and dibutylamine are here nearly as inactive as a non-electrolyte, glucose, dimethylamine and diethylamine a little more active, diamylamine very strongly active.

The following interpretation of this striking behavior may be suggested. In a porous system the ionic size determines the effect of an ion on the potential. Thus, ascending in the series, a decrease of the effect would be expected in such a system. This is what is true for the lower members. Then, with increasing length of the hydrocarbon chain, another property prevails, the hydrophobic character of the ions. This leads to their accumulation in the interface and thereby increases their activity, so to speak, by superposition of a concentration effect (Höber (1936)).

This interpretation may seem arbitrary to those who like to regard the cell membrane as a homogeneous non-aqueous layer and the objection may be made that instead of accumulation in the interface of a porous system, lipoid solubility may be assumed with equal justification, and the interpretation based on partition coefficients along the lines of either Osterhout's or Beutner's views. The latter interpretation fails, however, to explain the decreasing effect of the lower members, for the hydrophobic character alone would lead to an increase of effect throughout the whole series. The interfacial tension between an aqueous solution of dialkylamine and paraffin oil for instance, that may be taken as a measure of the hydrophobic character, decreases from the first member on. This is shown in Table I, where the number of $mm.^3$ per drop of dialkylamine solution formed from a stalagmometer in paraffin oil are listed. The assumption, therefore, that partition coefficients determine the effect of the ions, seems not adequate to account for the results described, unless the assumption of a mosaic membrane is made to explain the behavior of the lower members. Danielli (1935) has discussed the possible stability of such systems and found that their existence is not probable.

An accidental observation made when measuring the interfacial tensions shown in Table I may be mentioned shortly. If, instead of the non-ionized interface water / paraffin oil, the ionized interface

water / olive oil + oleic acid is used, the interfacial tension increases with increasing length of the hydrocarbon chain, instead of decreasing, as Table II shows. The explanation seems to be, that the interface active cations exert a discharging effect on the negatively charged interface, and that the increase of interfacial tension due to this discharge is greater than the decrease due to the molecular attraction

TABLE I

Interfacial Tension between Dialkylamine Solutions and Paraffin Oil

The salt solutions were N/50 in phosphate buffer N/72, pH 7.3.

Salt	mm.²/drop
NaCl	234
Dimethylamine	231
Diethylamine	219
Dipropylamine	201
Dibutylamine	168
Diamylamine	151

TABLE II

Interfacial Tension between Dialkylamine Solutions and a Mixture of Olive Oil and Oleic Acid 4:1

The salt solutions were N/50 in phosphate buffer N/72, pH 7.3.

Salt	mm.²/drop
KCl	78.5
Dimethylamine	80.5
Diethylamine	80.5
Dipropylamine	99
Dibutylamine	114
Diamylamine	127

across the interface. Since biological interfaces are probably mostly ionized, similar phenomena may have some biological importance.

If the interpretation given above is correct, it should be possible to test it on a porous model. Michaelis has shown that the dried collodion membrane is, in some respects, a useful model of the cell membrane. That it is a porous system was shown in several ways. Non-electrolytes that do not disrupt the structure of the membrane,

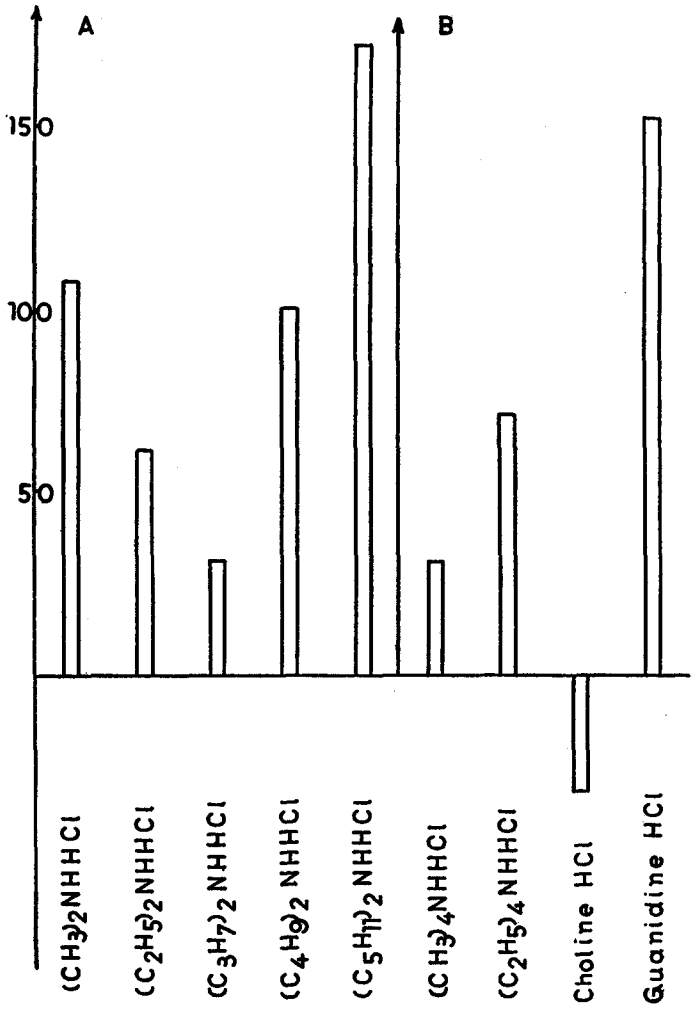

FIG. 6. Potential differences across collodion membranes between organic salts N/100 and NaCl N/100 (in per cent of the potential difference across the same membrane between KCl N/100 and NaCl N/100). Sign positive on the side of NaCl in the external circuit.

penetrate through the dried membrane according to their molecular sizes (Michaelis and Weech (1928)), and the transition from incompletely dried membranes, that doubtless contain pores, to the com-

pletely dried membranes is steady (Wilbrandt (1935)). The porous nature of this membrane may be regarded as certain, therefore.

Fig. 6 shows potential differences across dried collodion membranes between organic salts N/100 and sodium chloride N/100, in percentage of the potential difference measured between KCl N/100 and NaCl N/100. The dialkylamines show qualitatively the same behavior as on the nerve; in the lower part of the series the effect decreases with increasing length of the hydrocarbon chain, in the upper part from dipropylamine on, it increases (Fig. 6A).

It should be noted that the results obtained on collodion membranes with organic ions, are not as reversible as those obtained with inorganic ions. Only fresh membranes were used, therefore, in which case the results were reasonably reproducible. On each membrane, to obviate individual differences, the potential difference between KCl and NaCl was first measured and then the potential difference between the organic salt and NaCl. (Therefore the values in Fig. 6 are listed in percentage of the potential difference between KCl and NaCl.)

Of tetraalkylamines only tetramethylamine and tetraethylamine could be tested. Tetramethylamine had no lowering effect even in the concentration 3/4. It raised the potential by dilution of the potassium, less than a non-electrolyte (Fig. 7A), but more than dimethylamine (Fig. 7B). Thus, it is about as active as Na. Tetraethylamine is more active, it lowers the potential, (Fig. 7C and 7D), thus being more active than the corresponding dialkylamine, diethylamine (in contrast to the methyl-compounds). This is of some interest, because in his work on chemical stimulation J. Loeb (Loeb and Ewald (1906)) also found tetraethylamine effective but tetramethylamine ineffective. In his interpretation of chemical stimulation he assumed a primary effect of the stimulus on the membrane potential, which is in accordance with our results. It is, however, striking that Netter found no effect of tetraethylamine on the potential of frog nerves. On the other hand, our results on dialkylamines show that the effect of these ions is in general weaker on frog nerves than on crab nerves: dipropylamine and dibutylamine, on frog nerves are about as inactive as a non-electrolyte (Fig. 5B), whereas on crab nerves the first has a weak effect (but stronger than a non-electrolyte), the latter a rather

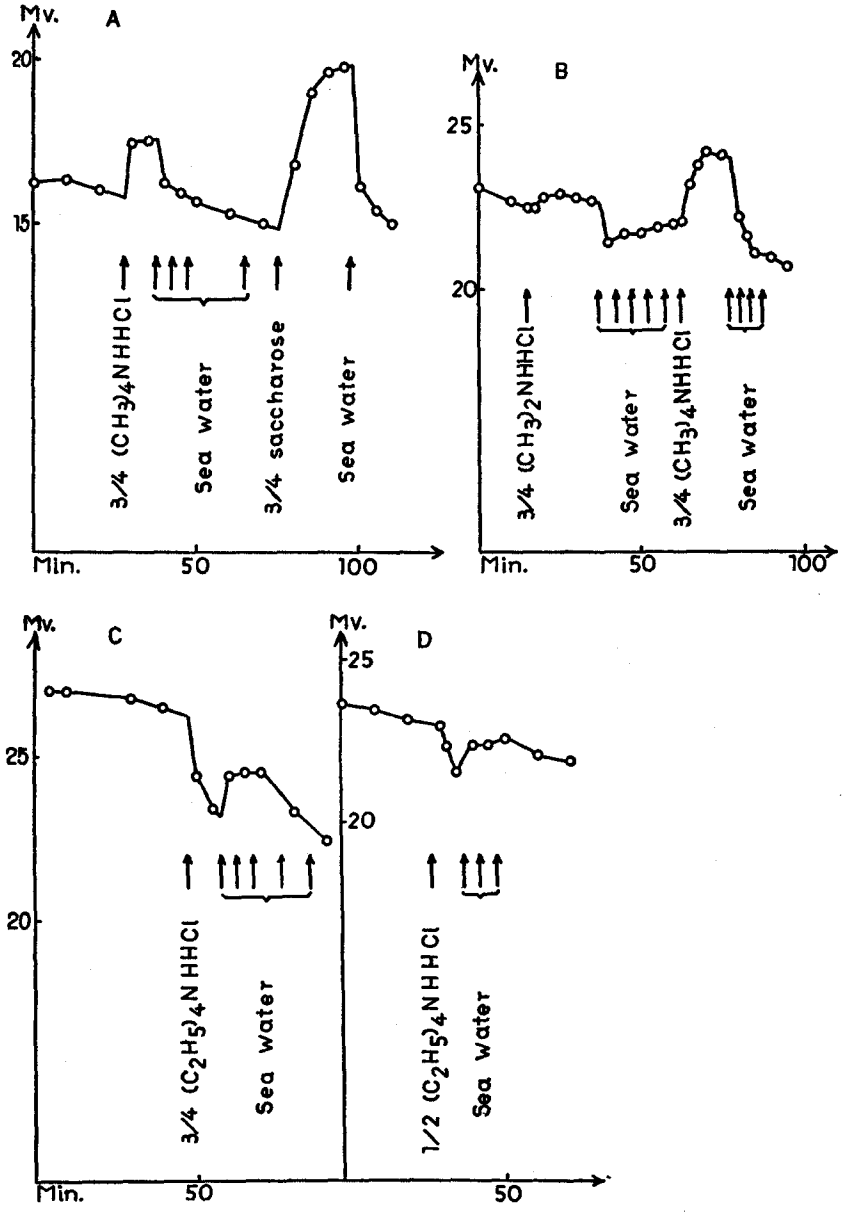

FIG. 7. Effect of tetraalkylamines on the potential of crab nerves

strong effect (Fig. 4C). The reason for this difference will be discussed later.

Guanidine has a strong effect; it lowers the potential even in the concentration 1/8 (Fig. 8A). Choline is about as active as Na. It raises the potential in the concentration 3/4 by dilution of potassium (Fig. 8B), but not as much as a non-electrolyte.

Also the tetraalkylamines, guanidine and choline, act very similarly on a collodion membrane, as Fig. 6B shows: tetraethylamine is stronger than tetramethylamine, guanidine very strong, choline very weak.

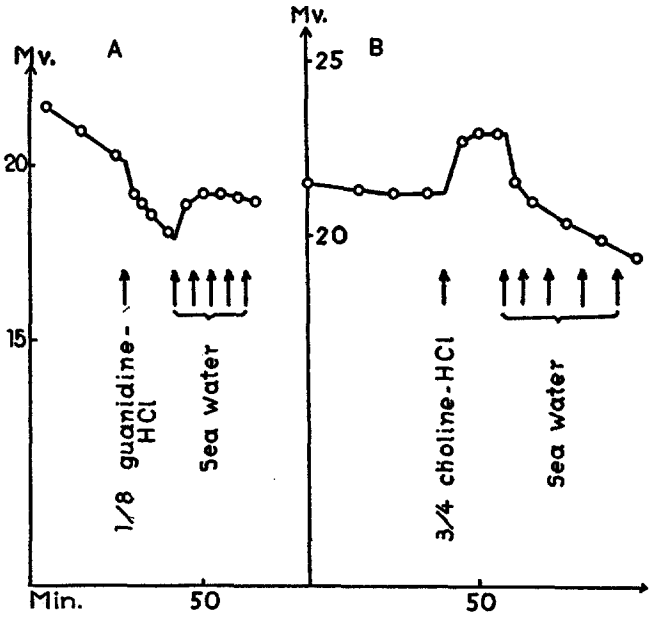

FIG. 8. Effect of guanidine and choline on the potential of crab nerves

Summarizing the results with organic cations, we may state that an influence of such ions on the nerve potential is definite. The effects range between that of Na and K, according to the approximate series: Li = Na = choline = tetramethylamine < dipropylamine < dimethylamine = diethylamine < tetraethylamine < guanidine < dibutylamine < diamylamine = K < Rb.

The effects are, however, not as reversible as those of the inorganic cations. Only after a very short application and in the lowest effective

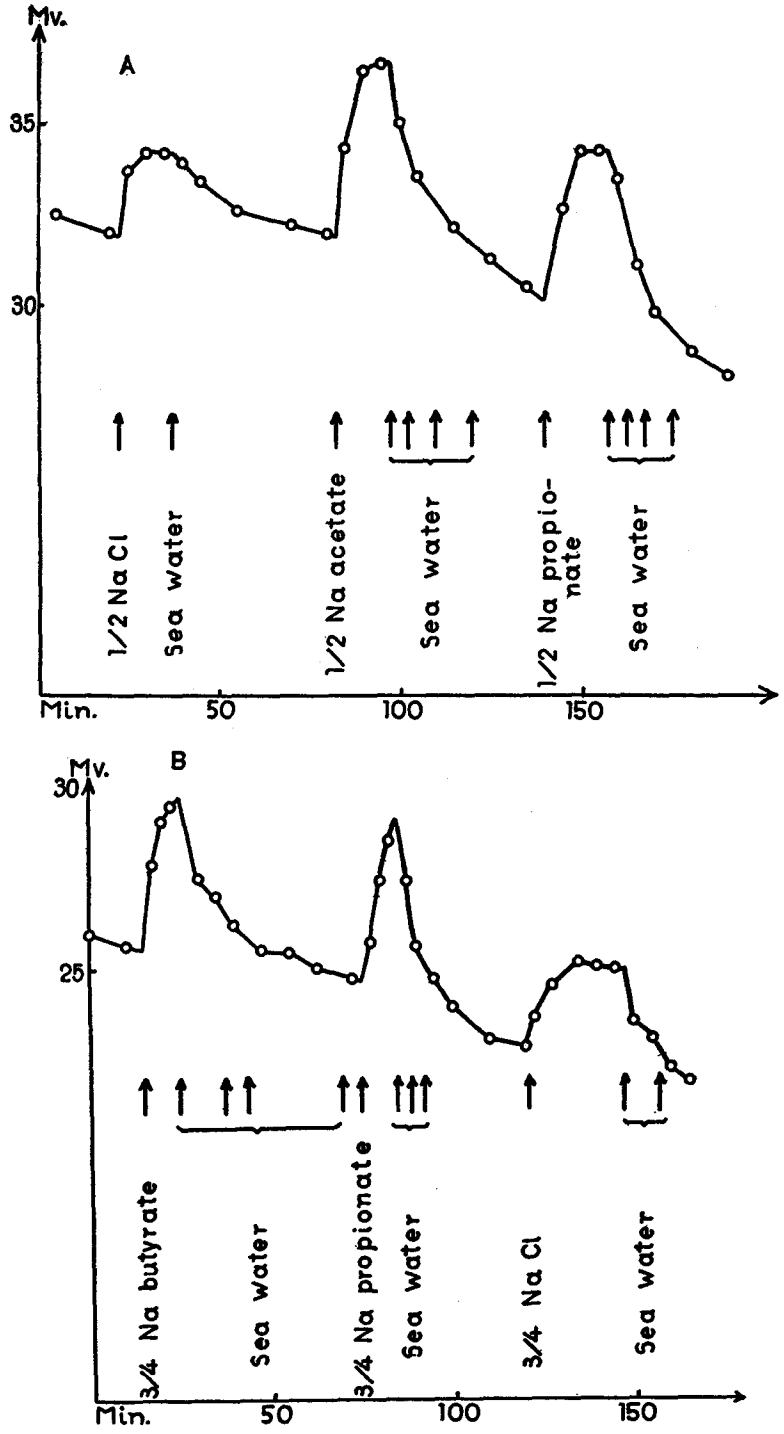

FIG. 9. Effect of fatty acids on the potential of crab nerves

concentrations is it possible to restore the original level of the potential. The effects resemble in a rather striking way those obtained on a porous model, the dried collodion membrane.

B. Anions.—Since an effect of inorganic anions on the potential could be shown, and since the formation of acids during metabolism is more frequent than that of bases, it appeared necessary for our problem also to test the influence of organic anions on the potential.

Sodium salts of fatty acids from acetate to butyrate were used,

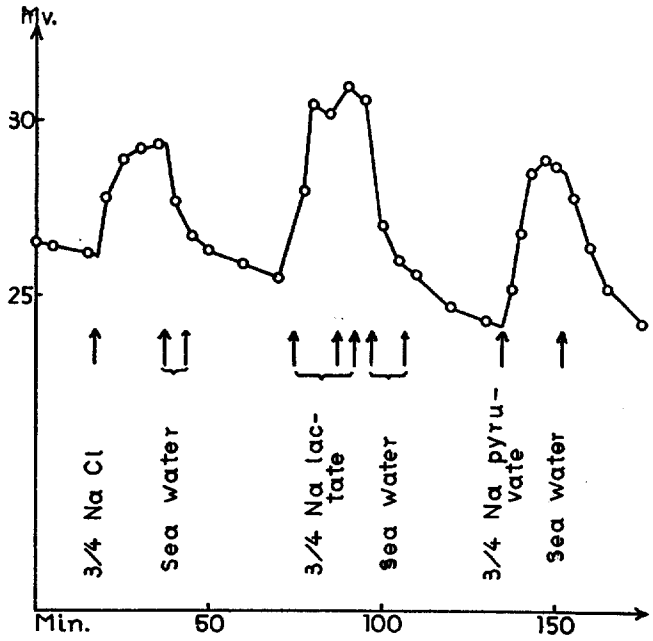

FIG. 10. Effect of lactate and pyruvate on the potential of crab nerves

furthermore lactate and pyruvate. Fig. 9 shows some records of the effect of these salts. They exhibit a weak, but definite effect. In high concentration they raise the potential more than is due to the dilution of potassium as a comparison with the effect of NaCl in the same concentration shows. The effect, thus, is similar to that of the active inorganic ions, NO_3 and SCN. A definite series among the fatty acids could not be established, their action was about equal. Higher acids could not be tested because they are too insoluble in sea water.

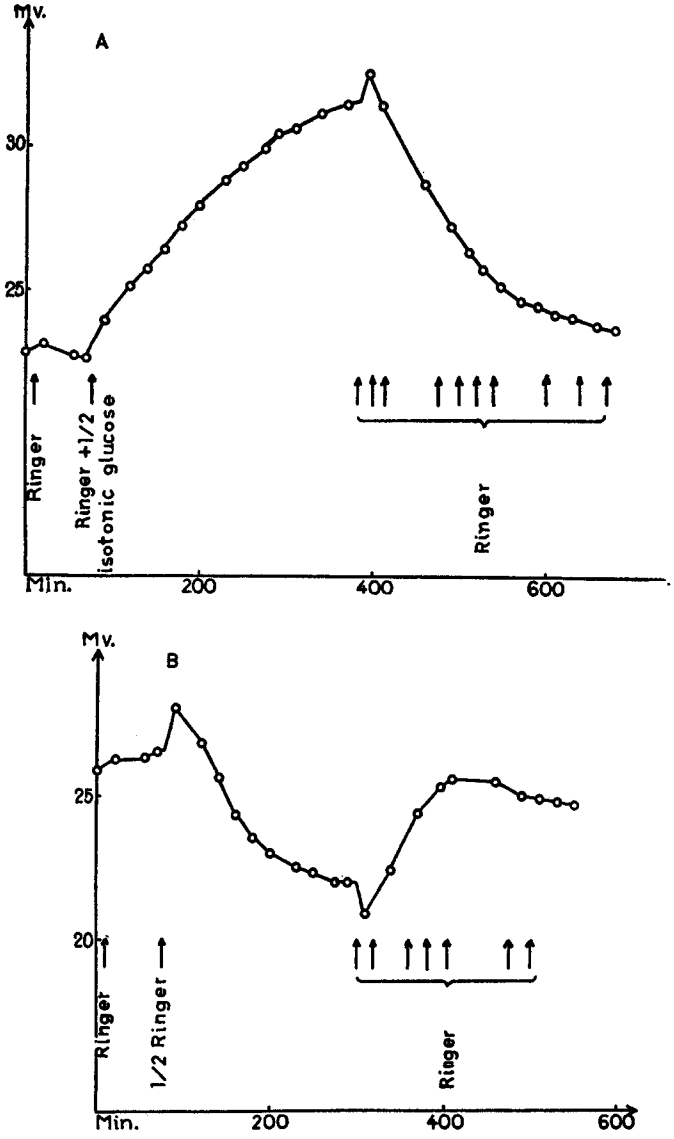

FIG. 11. Effect of varied osmotic pressure on the potential of the frog sciatic nerve.

Lactate and pyruvate were similarly active in high concentrations as Fig. 10 shows.

Summarizing we may state, that from the results also obtained with organic ions the assumption of a completely anion impermeable membrane around the nerve fiber cannot be supported. Organic anions have a weak, but definite effect on the potential.

The Effect of Varied Osmotic Pressure on the Potential of Frog Nerves

Netter (1926–27) found that the frog sciatic nerve behaves like an osmometer, following the Boyle-Mariotte law. This finding seemed to furnish a possibility to test the fundamental assumption that the potential is a membrane potential due to the difference of ionic composition on the two sides of the membrane. If this is the case, osmotic compression of the nerve should raise the ion concentration inside, and, if it remains unaltered outside, *i.e.* if the surplus osmotic pressure outside is exerted by a non-electrolyte, the potential should rise. A decrease of the outside osmotic pressure brought about by dilution of the outside medium should, on the other hand, be followed by an expansion of the nerve and a dilution of the inside ions to the same extent that the outside solution has been diluted. Since the inside cations are mainly or exclusively potassium ions and the outside ions mainly sodium, and since the concentration effect of potassium on nerve has been shown by Netter (1928) to be greater than that of sodium, the potential should fall. Previous to the fall, however, before the water shift is completed, the potential should, of course, rise, due to a mere concentration effect. Fig. 11 shows that both occur. This seems to indicate that the assumption of a membrane potential is correct.

It should be noted, that a similar effect on crab nerves could not be obtained. Since we know nothing about the osmotic properties of this nerve it is hard to interpret this negative result.

DISCUSSION

The results of this paper show a definite effect of organic ions, both cations and anions, on the membrane potential of the crab nerve. The efficacy of organic cations ranges between that of Na and K, that of anions is considerably weaker, but definite. The same is true for

inorganic anions. The membrane of crab nerves seems to be predominantly, but not exclusively, cation permeable similar to the findings of Höber for the membrane of muscles. The effects of organic ions are not as completely reversible as those of inorganic ions. If the ions are applied in the lowest effective concentration and only over a short time, however, the reversibility is complete.

A relation of parts of the electrical disturbance to the metabolism of the nerve by means of ionized metabolites therefore seems possible.

Whether the effect of ions formed inside the nerve fiber agrees with the effects described in this paper, where the ions were applied from outside, depends on whether the membrane is symmetric. This has mostly been tacitly assumed, for instance, when the effect of potassium from outside was used to interpret the resting potential as due to the high potassium concentration inside. The striking observations of Osterhout on the asymmetry of the membrane of *Valonia* and other large plant cells, however, have raised doubts. It should be pointed out, that in the latter case potential differences were measured across two cell membranes, whereas in the case of the nerve only one membrane is involved. The two cell membranes of *Valonia* are different and therefore the whole wall is asymmetric, but whether either of the two membranes is symmetric or not, we cannot judge from the experiments. Thus far there seems to be no evidence to indicate an asymmetry of a single cell membrane as far as the author knows.

Assuming the membrane to be symmetric, we may briefly discuss the possibilities of a connection between electrical disturbance and metabolism. It is not probable that the spike is due to the formation of metabolites. Formation of active anions in very high concentration would have to be assumed to explain the direction of the change, but quantitatively their efficacy would have to be so considerably greater than those reported in this paper, that the assumption seems improbable. Formation of acids, however, might be related to the negative after potential, disappearance of acids or formation of bases to the positive after potential, especially since the after potentials seem to have a connection with the metabolism.

The comparison of the non-myelinated and the myelinated nerve showed large agreement, but definite differences in some details. The effect of organic cations, as far as it was studied, was in general stronger

on crab nerves. Particularly striking is the case of dipropylamine and dibutylamine, also tetraethylamine, which seems entirely ineffective on frog nerves. The same is true for the effect of inorganic anions. It should be pointed out, however, that these differences are not necessarily due to differences of the cell membranes involved. It is entirely possible, that they are merely due to the fact that the salts are applied in one case in the presence of Ringer, in the other in the presence of sea water. The results reported here furnished some evidence that the hydrophobic character of the ions is important for their effect. This property is in general increased in a salt rich medium, for instance the solubilities of organic salts in sea water are mostly lower than in Ringer. It seems very likely, therefore, that the stronger effects of some organic ions on crab nerves in sea water are due to their increased hydrophobic character in this medium, in terms of our interpretation, to their increased interfacial accumulation.

We may state that a difference between the membranes that are the seat of the potential of non-myelinated nerves and myelinated nerves could not be shown definitely. Non-myelinated nerves of land animals should be investigated to clear up this point.

SUMMARY

1. The effect of osmotic pressure on the nerve resting potential of frog sciatic nerve is in accordance with the assumption of a membrane potential; increased osmotic pressure raises, decreased osmotic pressure lowers the potential.

2. The potential of crab nerves is affected by organic and inorganic cations in the approximate series:
Rb > K = diamylamine > dibutylamine > guanidine > tetraethylamine > diethylamine = dimethylamine > dipropylamine > tetramethylamine = choline = Na = Li.

3. The response of the potential to the series of dialkylamines (first decrease, then increase of response ascending in the series) is best understood by the assumption that the nerve membrane is a porous structure.

4. With respect to these salts as well as to other organic cations the dried collodion membrane as a model of a porous membrane shows a striking parallelism to the nerve membrane.

5. Both inorganic and organic anions (NO_3, SCN, acetate, propionate, butyrate, lactate, pyruvate) have a definite, if slight, effect in raising the potential of crab nerves. This effect of anions indicates that the nerve membrane is not completely anion impermeable.

6. The effect of organic ions is, with certain restrictions, reversible. Its possible relation to the resting potential and to the after potentials of the electrical disturbance is discussed.

7. The response of the myelinated sciatic nerve of the frog and of the non-myelinated nerve of the spider crab show considerable agreement. There are some definite differences which are, however, not necessarily due to differences of the cell membranes involved, but may be ascribed to the difference of ionic conditions in Ringer and sea water.

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