

The Action of Certain Polyvalent Cations on the Voltage-Clamped Lobster Axon

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ABSTRACT Calcium appears to be an essential participant in axon excitation processes. Many other polyvalent metal ions have calcium-like actions on axons. We have used the voltage-clamped lobster giant axon to test the effect of several of these cations on the position of the peak initial (sodium) and steady-state (potassium) conductance vs. voltage curves on the voltage axis as well as on the rate parameters for excitation processes. Among the alkaline earth metals, Mg^{+2} is a very poor substitute for Ca^{+2} , while Ba^{+2} behaves like "high calcium" when substituted for Ca^{+2} on a mole-for-mole basis. The transition metal ions, Ni^{+2} , Co^{+2} , and Cd^{+2} also act like high calcium when substituted mole-for-mole. Among the trivalent ions, La^{+3} is a very effective Ca^{+2} replacement. Al^{+3} and Fe^{+3} are extremely active and seem to have some similar effects. Al^{+3} is effective at concentrations as low as 10^{-5} M. The data suggest that many of these ions may interact with the same cation-binding sites on the axon membrane, and that the relative effects on the membrane conductance and rate parameters depend on the relative binding constants of the ions. The total amount of Na^{+} transferred during a large depolarizing transient is nearly independent of the kind or amount of polyvalent ion applied.

INTRODUCTION

Evidence has long been available that calcium ions are intimately associated with the mechanism of axon conduction (see Brink, 1954). Studies such as those of Höber (1920), and of Guttman (1940) showed that the resting potential and excitability of axons can be effectively maintained when certain other divalent cations, particularly those of the alkaline earth series, are substituted for calcium. The effects of alkali metal ions on nerve excitability have been reviewed by Narahashi (1966). Frankenhaeuser and Hodgkin (1957) studied the effects of calcium on the membrane ionic conductances of voltage-clamped squid axons. Recent studies by Dodge (1961) and by Takata et al. (1966 *b*) demonstrate that nickel and lanthanum have certain effects on the electrical properties of voltage-clamped axons which are qualitatively similar

to those of calcium. These similarities suggest the presence in the axon membrane of negatively charged sites with which calcium or its substituents interact and that the interaction plays a controlling role in the conduction process. It thus seems of interest to study in some detail the effects of a number of polyvalent cations on the electrical properties of axons using the voltage-clamped giant axon of the lobster. A preliminary report of some of these results has appeared (Blaustein and Goldman, 1966 *a*).

MATERIALS AND METHODS

The sucrose gap technique, voltage clamp and dissection method for the lobster giant axon have been previously described (Julian, Moore, and Goldman, 1962). Only

TABLE I
EFFECT OF POLYVALENT CATIONS ON
SODIUM AND POTASSIUM CONDUCTANCE VS.
MEMBRANE POTENTIAL CURVES

Ion	Sodium conductance†		Potassium conductance‡	
	ΔV_M Eq-Eq exchange with Ca^{+2}	ΔV_M ¶ Fivefold concen- tration change	ΔV_M Eq-Eq exchange with Ca^{+2}	ΔV_M ¶ Fivefold concen- tration change
	<i>mv</i>	<i>mv</i>	<i>mv</i>	<i>mv</i>
Ca^{+2}	— —	12 (17)	— —	10 (17)
Mg^{+2}	-10 (5)	10 (1)	-9 (5)	4 (1)
Co^{+2}	+9 (2)	— —	+17 (2)	— —
Cd^{+2}	+7 (4)	8 (2)	+23 (4)	13 (2)
Ba^{+2}	+7 (5)	— —	+13 (5)	— —
Zn^{+2}	+9 (1)	— —	— —	— —
Ni^{+2}	+12 (10)	12 (4)	+20 (10)	10 (4)
La^{+3}	+22 (12)	10 (4)	+37 (12)	21 (4)

† Sodium conductance at large depolarizations calculated as:

$$g_{Na}^* = \frac{I_{PI}}{V_M - V_{Na}}$$

where I_{PI} is the corrected peak initial current; V_{Na} is the apparent sodium equilibrium potential; i.e., the positive potential at which $I_{PI} = 0$, and V_M is the membrane potential.

‡ potassium slope conductance calculated as:

$$g_K^* = \frac{dI_{ss}}{dV_M}$$

where I_{ss} is the corrected steady-state current.

|| The magnitude of the shift of the normalized conductance vs. voltage curve along the voltage axis when an equimolar concentration of another cation is substituted for 50 or 60 mEq/liter of calcium. Positive values mean that the conductance curve is shifted in the direction of depolarization.

¶ The magnitude of the shift of the normalized conductance curve along the voltage axis when the polyvalent cation concentration is changed fivefold. Numbers in parentheses indicate the number of measurements.

axons with resting potentials greater than 95 mv, as measured in the sucrose gap, were voltage-clamped. Clamping (holding) potentials were greater than 100 mv and no correction was made for resting sodium inactivation (cf. Blaustein and Goldman, 1966 *c*).

The seawater used was Dalton's (1958) lobster solution, modified by the addition of 4 mM Tris(hydroxymethyl)aminomethane, adjusted to pH 7.4. This solution normally includes 50 mEq of calcium and 16 mEq of magnesium per liter. In most of our studies only a single polyvalent cation was used, as the chloride, at a concentration of 60 mEq per liter. In some instances, the polyvalent cation concentration was reduced to 12 mEq/liter and osmolarity maintained by the addition of sucrose. Control experiments showed that the sucrose had a negligible effect. In several experiments, the magnesium was not omitted and the various polyvalent cations were then used to replace the 50 mEq/liter of calcium in the controls. The solutions containing 60 mEq/liter of trivalent ion were slightly hypotonic since 20 mM of trivalent cation replaced 30 mM of CaCl_2 .

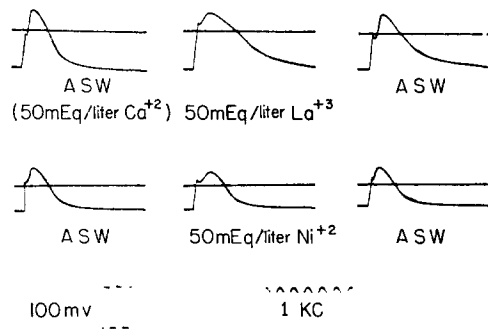


FIGURE 1. Axon L-50-65. $T = 5^\circ\text{C}$. Effects of La^{+3} and of Ni^{+2} at 50 mEq/liter on the action potential.

The voltage and current-time data were recorded on film and analyzed with the aid of a film-reading device and a digital computer. The current-time curves were corrected for leakage using as a basis the current-time curves from hyperpolarizing pulses and assuming that these were essentially linearly dependent on the voltage. These curves normally decay to a steady-state value with a time constant of the order of 0.3 msec (cf. Moore et al., 1966).

The reduced data were plotted as peak initial and steady-state currents, peak initial and steady-state conductances, and certain time parameters, all as functions of membrane potential. Peak initial conductances (g_{Na}^*) were referred to that potential at which the early transient current appeared to reverse direction (cf. Table I, first footnote). The steady-state conductances (g_{K}^*) were calculated as slope rather than chord conductances since the potassium equilibrium potential was not obtained (cf. Table I, second footnote). In certain solutions such as lanthanum seawater, the time to reach the steady state was greatly prolonged so that it was difficult to be certain that the steady-state values obtained were completely reliable. Thus, the actual values of g_{K}^* may sometimes have been greater than the measured values.

The time parameters used were the time from the beginning of the step to the peak transient current and the time required to reach two-thirds of the corrected steady-state value.

RESULTS

Effects on Action Potentials

In confirmation of studies by Moore et al. (1966) on the effects of lanthanum on the squid axon and those of Dodge (1961) on the action of nickel on the

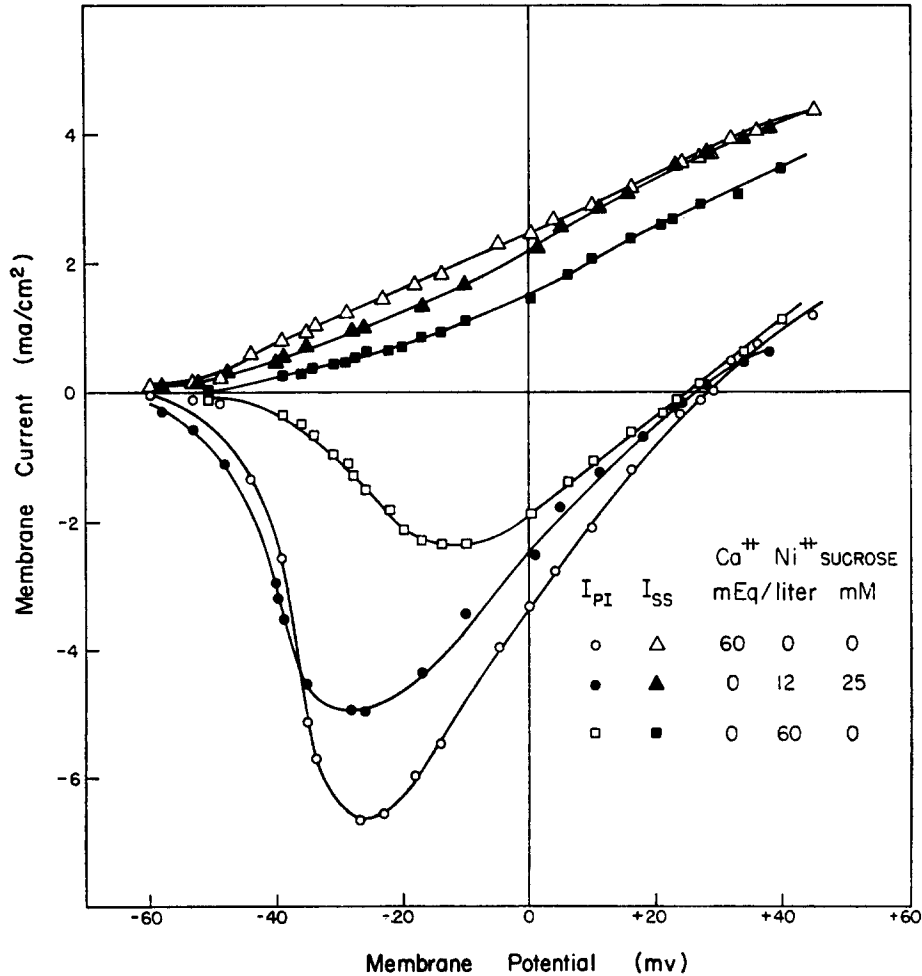


FIGURE 2. Axon L-58-65. $T = 7^{\circ}C$. Current-voltage curves for peak transient and steady state for normal calcium in artificial seawater and for two concentrations of Ni^{+2} substituted for the calcium.

frog node, both of these ions, when substituted for calcium in the lobster axon, slow the rates of rise and fall of the action potential (Fig. 1). Note that the voltage at the peak of the action potential is also somewhat reduced during treatment with either of these ions.

Effects on Ion Conductances

As has been shown in squid axons (Frankenhaeuser and Hodgkin, 1957), in myelinated fibers (Frankenhaeuser, 1957), and in lobster axons (Julian et al., 1962; Blaustein and Goldman, 1966 *b*), an increase in external calcium shifts the sodium conductance curve to the right along the voltage axis so that a larger depolarization step is needed to obtain any given level of conductance. Conversely, a reduction in external calcium shifts the conductance curve in the opposite direction. The maximum conductance is little affected by these changes. There is about a 10–12 mv shift along the voltage axis for a fivefold

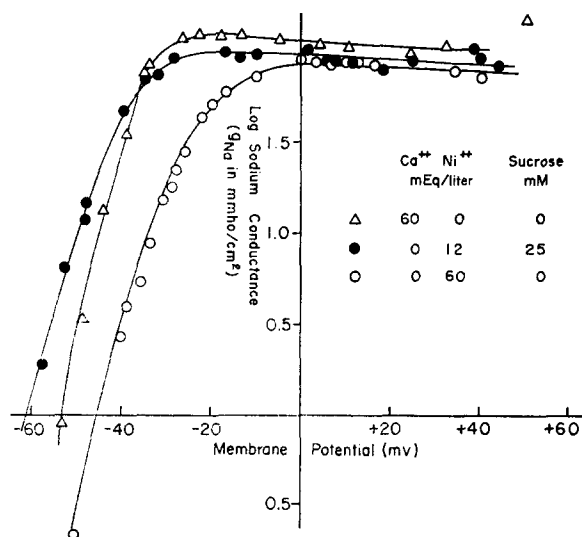


FIGURE 3. Axon L-58-65. $T = 7^{\circ}\text{C}$. Sodium conductance vs. membrane potential curves for the same artificial seawaters as in Fig. 2.

change in calcium concentration (6–8 mv per e-fold change). Similar effects also occur with respect to the potassium conductance.

Current-voltage relations for an axon in which nickel was substituted for calcium (Fig. 2) show that 12 mEq/liter of nickel appear to be a good replacement for 60 mEq/liter of calcium. On the other hand, the peak initial and steady-state current curves for the 60 mEq/liter of nickel resemble the curves one would expect to obtain with a large increase in external calcium. Data from this experiment plotted as sodium conductance vs. voltage (Fig. 3) indicate that while the curves for the 60 mEq/liter of calcium in the seawater and 12 mEq/liter of nickel in the seawater are nearly superposable, the sodium conductance curve for the 60 mEq/liter nickel seawater is shifted about 10 mv to the right along the voltage axis. This is roughly where one would expect the curve to lie for a four- to fivefold increase in calcium concentration as compared with the normal concentration. When 60 mEq/liter of

magnesium are substituted for calcium (Table I), the sodium conductance curve shifts about 10 mv to the left along the voltage axis, roughly paralleling a fivefold decrease in external calcium. If the magnesium concentration is then reduced fivefold, there is a further 10–12 mv shift to the left. Corresponding data were obtained for several other ions (Table I).

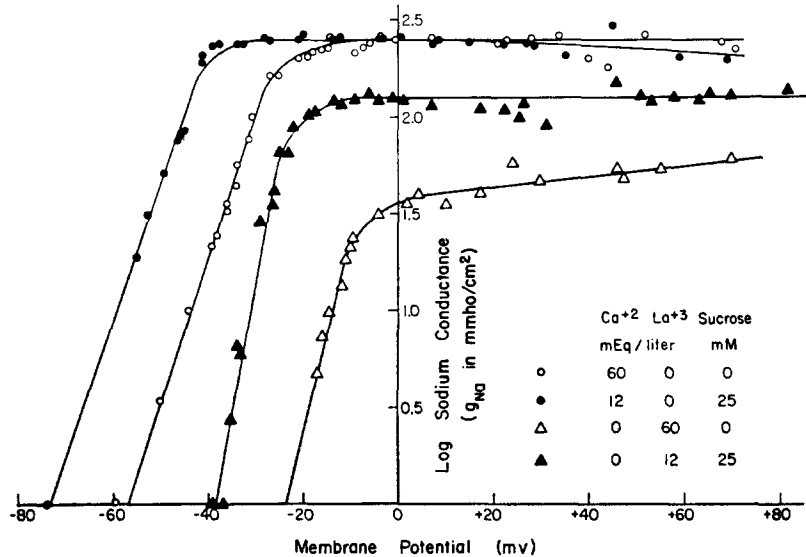


FIGURE 4. Axon L-56-65. $T = 5^{\circ}\text{C}$. Sodium conductance vs. membrane potential with calcium or lanthanum in artificial seawater at indicated concentrations.

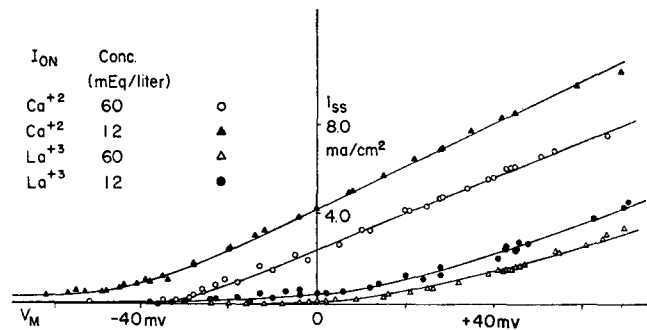


FIGURE 5. Axon L-56-65. $T = 5^{\circ}\text{C}$. Steady-state current vs. membrane potential with calcium or lanthanum in artificial seawater at indicated concentrations.

Ions which, when substituted for calcium on a mole-for-mole basis act like high calcium, often seem to produce a decrease in the maximum sodium conductance (plateau level of the conductance curve). This is also noticeable to a slight extent with high concentrations of calcium itself (Takata et al., 1966 *a*; Blaustein and Goldman, 1966 *b*). In order to separate the horizontal

shifts in the conductance curves from the vertical shifts (depression of conductance), we have measured the horizontal shifts after displacing the sodium conductance curves vertically to make the plateau regions coincide. When this is done, it turns out that 60 mEq/liter of cadmium shift the sodium conductance curve about 5 mv to the right along the voltage axis. On the other hand, a fivefold reduction in cadmium concentration shifts the curve 8–10 mv to the left along the voltage axis. When lanthanum is substituted for calcium

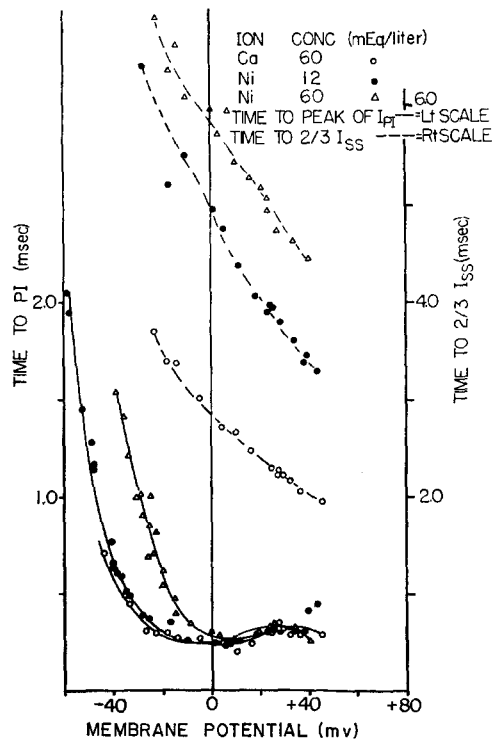


FIGURE 6. Axon L-58-65. $T = 7^{\circ}\text{C}$. Time parameters vs. membrane potential for axon in calcium and in nickel solutions.

(equivalent-for-equivalent) even larger displacements are found (Fig. 4), although the shift due to changes in the concentration of lanthanum ion itself is approximately the same as for the other polyvalent ions.

The effects of two concentrations of lanthanum and two concentrations of calcium on the steady-state current vs. voltage curve are shown in Fig. 5. The curve shifts progressively to the right as the calcium concentration is increased from 12 mEq/liter calcium to 60 mEq/liter, then exchanged for 12 mEq/liter of lanthanum, and then the latter is increased to 60 mEq/liter. The maximum slope conductance (i.e., the slope of the current-voltage curve at large depolarization steps) is only slightly reduced in the lanthanum solutions.

Table I summarizes some of these effects. Note that all the ions tested give roughly a 10–12 mv shift in the sodium conductance curve along the voltage

axis for a fivefold concentration change. For the most part, this also holds true for the potassium conductance curve (cf. Figs. 2 and 5). The apparently large deviations in the steady-state conductances during lanthanum treatment (Table I) are in part attributable to the smaller ratio of Na and K currents to the leakage current, and to the possibility that a "steady state" may not have been reached by the end of a 10 or 20 msec pulse.

The data in Table I also show that replacement of one ion by another (equivalent-for-equivalent) shifts the conductance curves to a varying degree.

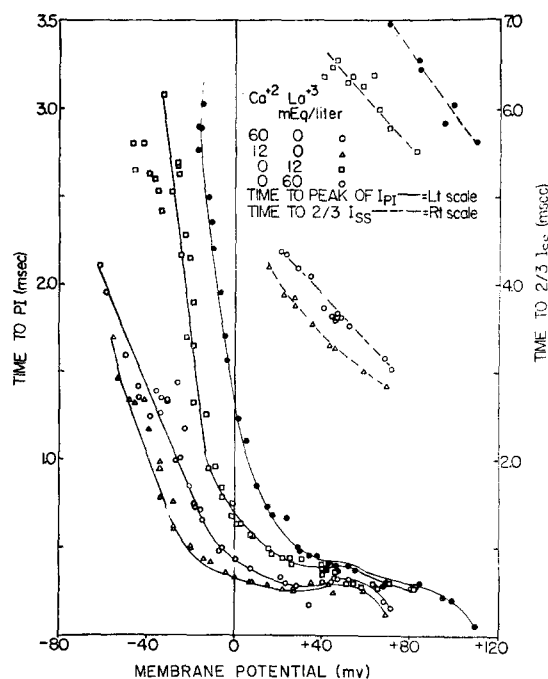


FIGURE 7. Axon L-56-65. $T = 5^{\circ}\text{C}$. Time parameters vs. membrane potential for axon in calcium and in lanthanum solutions.

Magnesium, for example, shifts the sodium conductance curve about 10 mv to the left; whereas the other ions shift the sodium conductance curve to the right. The effects of cobalt, cadmium, barium, and zinc are equivalent to about a three- to fourfold increase in calcium concentration; while nickel is about 5 times and lanthanum 20–25 times as effective as calcium. In a few instances, two polyvalent cations (e.g., calcium and nickel or calcium and lanthanum) were present in the seawater and the effects of these ions on the conductance curves appeared to be additive (cf. Dodge, 1961).

Effects on Time Parameters

An obvious effect of nickel and lanthanum, for example, on the action potential is a slowing of the rates of both rise and fall. Time parameter data for Ni^{+2} and La^{+3} are shown as functions of the membrane potential in Figs. 6 and

7. Most of the ions tested when substituted for calcium mole-for-mole appear to displace these curves to the right; i.e., they increase the time to the peak and to two-thirds of the steady state at a given membrane potential. A similar effect is produced by raising polyvalent ion concentration (Frankenhaeuser and Hodgkin, 1957; Goldman and Blaustein, 1966). Magnesium displaces the curves to the left as does the lowering of the polyvalent cation concentration (Figs. 6 and 7).

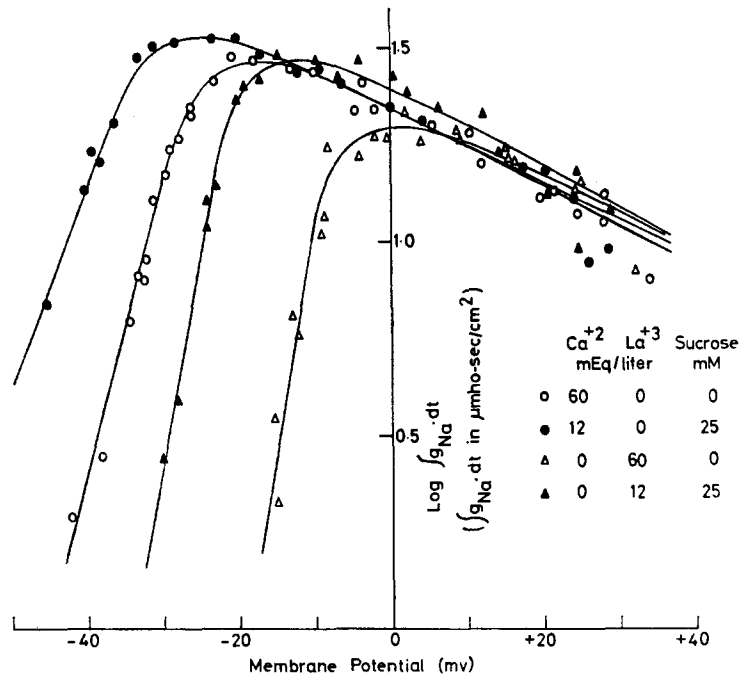


FIGURE 8. Time integrals of sodium conductance vs. membrane potential. Same axon as in Fig. 4. See text for method of calculation.

The multiple effects of these different ions may be further analyzed by calculating the time integrals of the transient current. These represent approximately the amount of sodium transferred during the lifetime of the transient.¹ Using lanthanum as an example, the data have been plotted (Fig.

¹The time integrals were calculated from the early transient part of the current-time curves after subtraction of the leakage currents. Because a single axon rarely lasts more than an hour, and because the time required to change solutions, reach a steady state, and perform a voltage-clamp run takes about 10 min, the separation of sodium and potassium contributions to the early current was not carried out. If, as the data in Table I suggest, the time- and voltage-dependent parameters for sodium and potassium are affected by about the same amount, we would expect that at large depolarizing voltages the relative contributions of the late (potassium) conductance to the early transient should remain about the same when the polyvalent ion, or its concentration, is changed.

8) in terms of conductances rather than currents, i.e.

$$\int I_{Na} dt = (V_m - V_{Na}) \int g_{Na} dt$$

where V_m is the step potential and V_{Na} is the potential at which the early current reverses direction. The integration has been carried out over the duration of the transient. Despite the apparent concentration-dependent depression of sodium conductance by lanthanum (cf. Fig. 4), the sodium transferred at large depolarizations appears to be unaffected by the substitution of lanthanum for calcium, and is independent of the polyvalent cation concentration.

In addition to La^{+3} , several other trivalent cations have been tested, in-

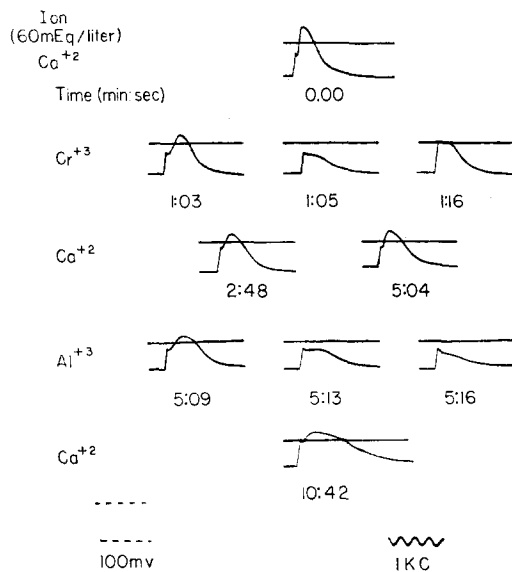


FIGURE 9. Axon L-62-65. $T = 7^{\circ}C$. Effect on action potential of substitutions of Cr^{+3} or Al^{+3} for calcium. Numbers under tracings are times (in minutes and seconds) after the start of the experiment.

cludign Al^{+3} , Cr^{+3} , and Fe^{+3} . When substituted for Ca^{+2} on an equivalent-for-equivalent basis, these ions block the action potential. The effects are reversible if the trivalent ion is washed out within a minute or less (Fig. 9). A significant effect of Al^{+3} may be obtained when this ion is added to normal seawater at concentrations at least as low as 0.03 mEq/liter. There is also a marked reduction of early transient current resulting from the addition of 0.03 mEq/liter of Al^{+3} to seawater. This ion also reduces the steady-state current. Cr^{+3} and Fe^{+3} have similar effects on the voltage-clamped axon. These trivalent ions also appear to delay the time-to-peak but the effects are partially obscured by the large reduction in the magnitude of the currents.

DISCUSSION

It is clear that a large number of polyvalent cations can replace calcium in the environmental medium in the sense that the axon may remain excitable and give rise to voltage clamp curves which qualitatively resemble those of

axons in a normal medium. There are, however, important quantitative differences. The current-time curves appear to be, roughly at least, stretched out or shrunken along the time scale, as well as along the amplitude scale. For myelinated fibers, there is considerable evidence (Del Castillo-Nicolau and Hufschmidt, 1957; Dodge, 1961; Takahashi et al., 1960; Meves, 1963) that several polyvalent cations including nickel and cobalt increase the duration of the action potential just as they do in the present studies. However, the list of ions tried is by no means complete. We have used Mg, Ca, Ba, Zn, Co, Ni, and Cd among divalent ions and Al, La, Cr, and Fe among trivalent ions. There are many more, but except when they have a strong heavy metal poisoning or other special effect, such as may be produced by Pb or Hg, most polyvalent ions could be expected to behave similarly. It should be noted that Al, Cr, and Fe are so effective as to raise the question whether they behave only as calcium replacements even though trivalent ions may be expected to be more potent, possibly because of the greater charge. In this respect, more work needs to be done.

The marked similarity of qualitative effects of these ions strongly suggests that if there are anionic sites in the membrane which are essential participants in the excitability control mechanisms, any of these ions may interact with these sites in a similar fashion. The quantitative differences can be attributed primarily to differences in the rate constants of association and dissociation for the various cations. Further, dissociation of the site-cation complex may well be a first step in the changes subsequent to membrane depolarization. Thus, for example, an increase in the time parameters for the transient and steady-state currents could arise from a relative decrease in the dissociation rate constant and this would then lead to a lengthened action potential. If the "sodium-on" process is slowed more than the "sodium-off" process, there would also be a decrease in the plateau value of the sodium conductance, even though, as has been shown, the total sodium transferred during a transient remains nearly unchanged at large potential steps. This lack of effect of polyvalent cations on sodium transfer may be contrasted with the action of certain anesthetics such as tropines or barbiturates, which reduce sodium transfer at all membrane potentials (Blaustein, unpublished data). A possible interpretation of this phenomenon would be that polyvalent ions affect the speed of operation and the voltage response of the mechanisms that control the flow of Na and K without, however, reducing the total number of sites involved. The anesthetics, on the other hand, may also reduce the number of available sites. However, more data are needed before any definite conclusions can be drawn.

We have also found that although each ion has its own degree of relative activity, the displacement of the conductance curves per fractional change of ion concentration is nearly the same for all the ions tested. This may be inter-

preted in the following way. When the axon is sufficiently polarized, both the sodium and potassium conductances appear to be exponential functions of the potential. They are then also approximately inversely proportional to the concentration of the polyvalent ion and independent of its binding strength. However, when the ion is changed, so is the binding constant and with it the position of the conductance curve on the voltage axis. The amount of displacement should also be related to the value of any coefficient which occurs in the exponent (see Frankenhaeuser and Hodgkin, 1957; Goldman, 1964).

In the presence of more than one ion species, competition for the sites should occur. It has been shown (Blaustein and Goldman, 1966 *b*) that calcium and procaine appear to compete for these anionic sites. We would expect that other polyvalent cations would likewise compete. The data obtained by Khodorov and Beliaev (1964) and Takahashi et al. (1960) indicating that Ni, Cd, and Co interact with procaine in the frog myelinated fiber are thus consistent with the view expressed here. Carvalho and Sandow (1966) and Sandow and Isaacson (1966) have discussed similar effects on the excitation and contraction of muscle. In addition, a number of polyvalent ions have been shown to compete both with each other and with procaine for binding to phospholipids in vitro (Blaustein, 1967). It would be very useful to know the binding parameters for each ion. The material presented here gives only a rough indication; more data are required for characterizing the anionic sites and for helping in their exact identification.

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