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OBSERVATIONS ON ROD COUPLING IN THE ISOLATED RETINA OF *BUFO MARINUS*

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Abstract—Rod coupling was studied in the superfused isolated retina of *Bufo marinus*. Pairs of interacting rods were simultaneously impaled; current injected into one rod caused a current-induced potential in the second rod. Current-induced potentials and input resistance were monitored while changing the superfusate. Interactions were not reduced by removing extracellular Na^+ or Cl^-, indicating that these conductances do not mediate coupling. Interactions were not eliminated by altering extracellular Ca^{2+} or decreasing intracellular pH; the interactions are thus resistant to treatments that uncouple cells in other systems.

INTRODUCTION

Two lines of evidence have shown that rods interact with each other in the retina. First, the response properties of a single rod depend in part on the amount of light falling on neighboring rods (Schwartz, 1973, 1975, 1976; Fain, 1975; Fain *et al.*, 1976; Lamb and Simon, 1976; Leeper *et al.*, 1978; Gold, 1979; Griff, 1979; Griff and Pinto, 1981). Secondly, interactions between rods have been studied directly by simultaneously impaling pairs of rods; current injected into one rod causes a potential change of like sign in the other rod (Copenhagen and Owen, 1976a, b, 1980; Werblin, 1978; Attwell and Wilson, 1980; Griff and Pinto, 1981). Much evidence suggests that rods interact via electronic coupling. Anatomical studies show that gap junctions exist between rod inner segments (Gold and Dowling, 1979; Custer, 1973). Pharmacological studies show that the response of a single rod to diffuse stimulation is not affected by administration of cobalt, a potent inhibitor of chemical synaptic transmission (Schwartz, 1976; Copenhagen and Owen, 1976a). The amplitude of the current-induced potential also is not reduced by Co^{2+} (Werblin, 1978; Griff, 1979). The ionic dependence of current-induced potentials, however, is not known.

We have studied the effects of various test solutions on coupling between simultaneously impaled pairs of rods in the isolated retina. We examined the possible involvement of sodium, potassium, or chloride conductance in the coupling pathway by monitoring current-induced potentials while changing the superfusate to one that had altered concentration of one of these ions. We also observed the effects of treatments known to uncouple gap junctions in other systems.

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METHODS

All experiments were performed on the isolated retina of *Bufo marinus*. The retina was mounted receptor-side-up in a 0.4 ml chamber and continually superfused with oxygenated modified Ringer's solution. Table 1 gives the composition of the normal Ringer's and all test solutions used.

Solution changes were made by switching a three-way valve. The time required to change the solution in the recording chamber was measured by two methods. In one case the test solution contained a dye, and the time-course of the change in transmission of light through the perfusion chamber was measured with no retina present. In a separate experiment with the retina in the perfusion chamber, the solution was switched from the normal Ringer's to a test solution in which the free Ca^{2+} concentration was buffered to 10^{-8} M with EDTA. The time-course of the change in calcium concentration above the rod outer segments was measured with a calcium selective electrode. Both methods revealed that the solution change was 90% complete within 60 sec. Figure 1 shows the time-course of a solution change using the first method.

The preparation was viewed under IR illumination using an IR image intensifier (Varo 8586/3). Two microelectrodes were mounted on separate manipulators and positioned 20–50 μm apart above the tips of the outer segments. Each electrode was advanced independently until each had impaled a rod; electronic oscillations were produced at the tip of the electrode to facilitate impalement. In successful impalements the membrane potential of each rod, measured in normal Ringer's before and after application of the test solution, did not change more than 5 mV, and the light response did not vary more than 20%.

After impaling two rods simultaneously, hyperpolarizing current (-1 nA) was injected alternately into each rod through the microelectrode. For the pair of rods to constitute an *interacting pair*, a

Table 1. Solutions

Solution	$CaCl_2$	$MgCl_2$	KCl	NaCl	EDTA	Other
Control	0.86	1.3	2.4	108	—	
A. Na^+-free	0.86	1.3	2.4	0	—	Choline Cl^- 108
B. 100% CO_2	0.86	1.3	2.4	0		$NaHCO_3$ 108
C. Propionate	0.86	1.3	2.4	0		Na^+ prop. 108
D. 0.21 mM Ca^{2+}	0.21	1.3	2.4	108	—	
E. 10^{-8} M Ca^{2+}, TMA-Cl for NaCl	1.0	0	0	0	2.0[a]	TMA-Cl 108
F. 10^{-8} M Ca^{2+}, Raffinose for NaCl	1.0	0	0	0	2.0[a]	Raffinose 216
G. 10^{-8} M Ca^{2+} (w/EGTA)	1.0	1.3	0	0	EGTA 2.0[a]	TMA-MS 108
H. 7X control Ca^{2+}	6.02	1.3	2.4	108	—	
I. 14X control Ca^{2+}	12.04	1.3	2.4	108	—	

All solutions contained glucose (5 mM) and HEPES (2.8 mM) adjusted to pH 7.78 with NaOH (or with KOH in Na^+-free solution).

[a]Adjusted to pH 7.8 with Tris-base and KOH (2.4 mM).

hyperpolarizing current injected into one rod had to cause a detectable hyperpolarization (limit of detectability = 0.5 mV) in the other rod of the pair. Interactions were demonstrated in over 175 pairs of rods. The amplitude of the current-induced potential was measured as the difference between the voltage immediately before the current pulse and the voltage immediately before the current was turned off. From the angle at which each microelectrode was advanced and the distance the electrode traveled from the surface to the impaled rod, we calculated the separation between impaled rods of 20 interacting pairs; the mean separation was 30 μm. No correlation was found, however, between the amplitudes of the current-induced potentials and the calculated cell separations.

To measure the magnitude of the input resistance, single rods were impaled with double-barreled pipettes made from capillary with θ-shaped cross-section (1:1 ratio of septum-to-wall thickness). These pipettes had a resistance of 300–600 MΩ and a time-constant of 10–50 msec. Current pulses of each of several different amplitudes were injected through one barrel of the pipette and the plateau voltage in the other barrel was measured. Input resistances were calculated by dividing the amplitude of the voltage by

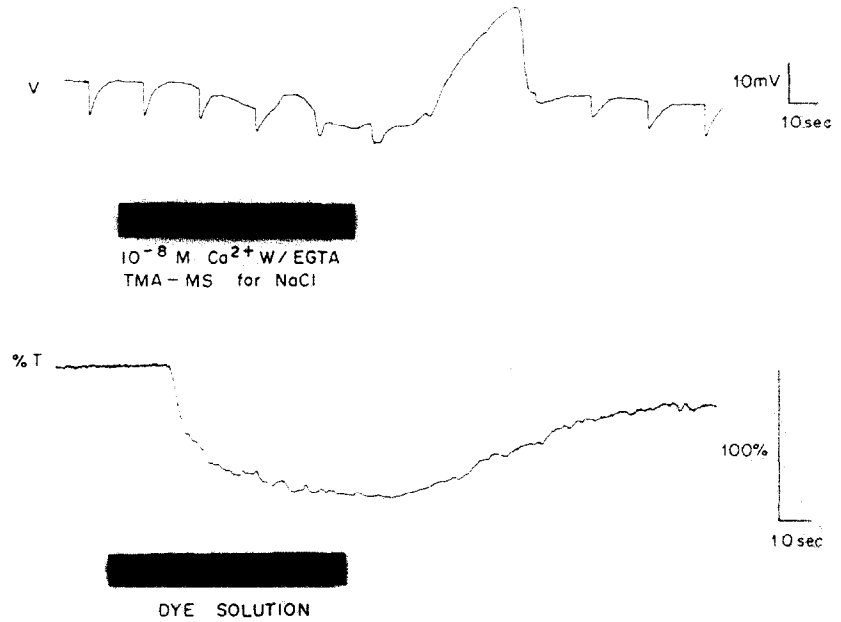

Fig. 1. The time-course of a solution change. Top: a single rod was impaled and its membrane potential monitored as shown by trace V; a 200 msec stimulus was presented every 17 sec. When the preparation was superfused with a test solution (G, Table 1) in which the free $[Ca^{2+}]$ was buffered to 10^{-8} M with EGTA, and in which tetramethylammonium methanesulfonate (TMA–MS) was substituted for NaCl, the membrane hyperpolarized and the responses to light were diminished. Bar denotes application of test solution. The large potential change on return to normal Ringer's is not completely understood. Bottom: the transmittance through the perfusion chamber (no retina present) was monitored as shown by trace T. A dye solution was introduced by switching a valve and the time period in which the valve to the dye solution was open is indicated by the bar.

the amplitude of the injected current. The coupling resistance between the two barrels was less than 3% of the measured input resistance. For these measurements, hyperpolarizing currents were generally used because the current–voltage relationship of the cell is approximately linear for membrane voltages that are hyperpolarized with respect to dark resting voltage (see Fig. 5, Bader *et al.*, 1979; Werblin, 1979; Attwell and Wilson, 1980).

RESULTS

Injection of hyperpolarizing or depolarizing current into one rod of an interacting pair caused a potential change (current-induced potential) of the same polarity in the other rod (Copenhagen and Owen, 1976, 1980; Werblin, 1978; Attwell and Wilson, 1980; Griff and Pinto, 1981). The injection of a given hyperpolarizing current into a rod caused a larger current-induced potential than did a depolarizing current of the same magnitude, regardless of which rod of an interacting pair was injected with current.

Application of a test solution could change the amplitude of the current-induced potentials by altering the junctional (coupling) resistance and/or the non-junctional membrane resistance. A solution-induced decrease of current-induced potentials and an increase of the input resistance can be most simply explained by an increase in junctional resistance. A decrease in current-induced potentials accompanied by a decrease in input resistance can be explained by a decrease in non-junctional resistance. The relative effects of a test solution upon junctional and non-junctional resistance, however, could not be quantified in the present experiments (see Discussion).

Decreased extracellular $[Na^+]$ *and* $[Cl^-]$

If changes in sodium conductance contributed significantly to the current-induced potentials, their amplitudes should have been reduced by lowering $[Na^+]_0$. Furthermore, since lowering $[Na^+]_0$ causes the rod membrane to hyperpolarize toward the potassium equilibrium potential, E_K, the driving force on K^+ will also be reduced [although not eliminated, since the membrane might not hyperpolarize to E_K (Capovilla *et al.*, 1981)]. Thus, if changes in potassium conductance contributed significantly to the current-induced potentials, their amplitudes should also have been reduced in the Na^+-free test solution.

Interacting pairs of rods were impaled in normal Ringer's. When the retina was bathed in Na^+-free test solution (Solution A, Table 1), the membrane of both rods hyperpolarized and the responses to light were reduced. The amplitudes of the potentials induced by hyperpolarizing current (plateau value, see Methods) were unaffected by bathing the retina in the Na^+-free test solution (6 pairs, see Fig. 2a). Upon return to normal Ringer's, the membrane potentials repolarized and the responses to light returned to their pretest values. The potentials induced by depolarizing currents increased in the test solution (Fig. 2b).

If changes in chloride conductance contributed significantly to the current-induced potentials, their amplitudes should have been reduced by lowering $[Cl^-]_0$. To explore this possibility, we replaced $[Cl^-]_0$ with propionate (Solution C, Table 1). The test solution caused a hyperpolarization of the membrane in the dark but caused little change in the amplitudes of the current-induced potentials (Fig. 3). Similar results were observed when Na^+-acetate or Na^+-methane sulfonate replaced sodium chloride (5 pairs).

Decreased intracellular pH

Decreasing intracellular pH has been shown to abolish ionic communication between cells (Turin and Warner, 1977, 1980; Bennett *et al.*, 1978; Rose and Rick, 1978; Giaume *et al.*, 1980; Korn, 1980). We therefore evaluated the effects of treatments that have been shown to decrease the intracellular pH of other cells. One such treatment is to superfuse the cell under study with a bicarbonate-buffered solution that is equilibrated with 100% CO_2 (Boron and DeWeer, 1976; Thomas, 1976; Turin and Warner, 1980). Interacting pairs of rods were impaled in normal Ringer's. The solution was then switched to the test solution equilibrated with 100% CO_2 (Solution B, Table 1). The membranes of both cells hyperpolarized and the light responses became smaller, but the amplitudes of the current-induced potentials did not decrease (4 interacting pairs, hyperpolarizing pulses only). Upon return to normal Ringer's, the membranes repolarized but the light responses remained diminished; again, the current-induced potentials remained unchanged (see Fig. 4). One retina was bathed in the CO_2 test solution for up to 5 min with no resulting decrease in the amplitudes of the current-induced potentials. Replacement of chloride by propionate or isethionate causes an increase in coupling resistance of the crayfish electrotonic synapse (Asada and Bennett, 1971), presumably also due to a decrease of intracellular pH caused by influx of the weak acid (Roos and Boron, 1981, pp. 344–345). As described above, replacement of Cl^- with propionate, acetate or methane sulfonate did not decrease the amplitudes of the current-induced potentials.

Increased and decreased extracellular $[Ca^{2+}]$

Changes in intracellular free $[Ca^{2+}]$ have been shown to be correlated with changes in cell coupling (see Lowenstein, 1981 for review). We tried to increase $[Ca^{2+}]_i$ by increasing the extracellular calcium concentration, $[Ca^{2+}]_0$. When normal Ringer's was replaced by a test solution containing 7 times normal $[Ca^{2+}]_0$ (Solution H, Table 1), the membranes of both rods became hyperpolarized, and the responses to light were diminished (Brown and Pinto, 1974). How-

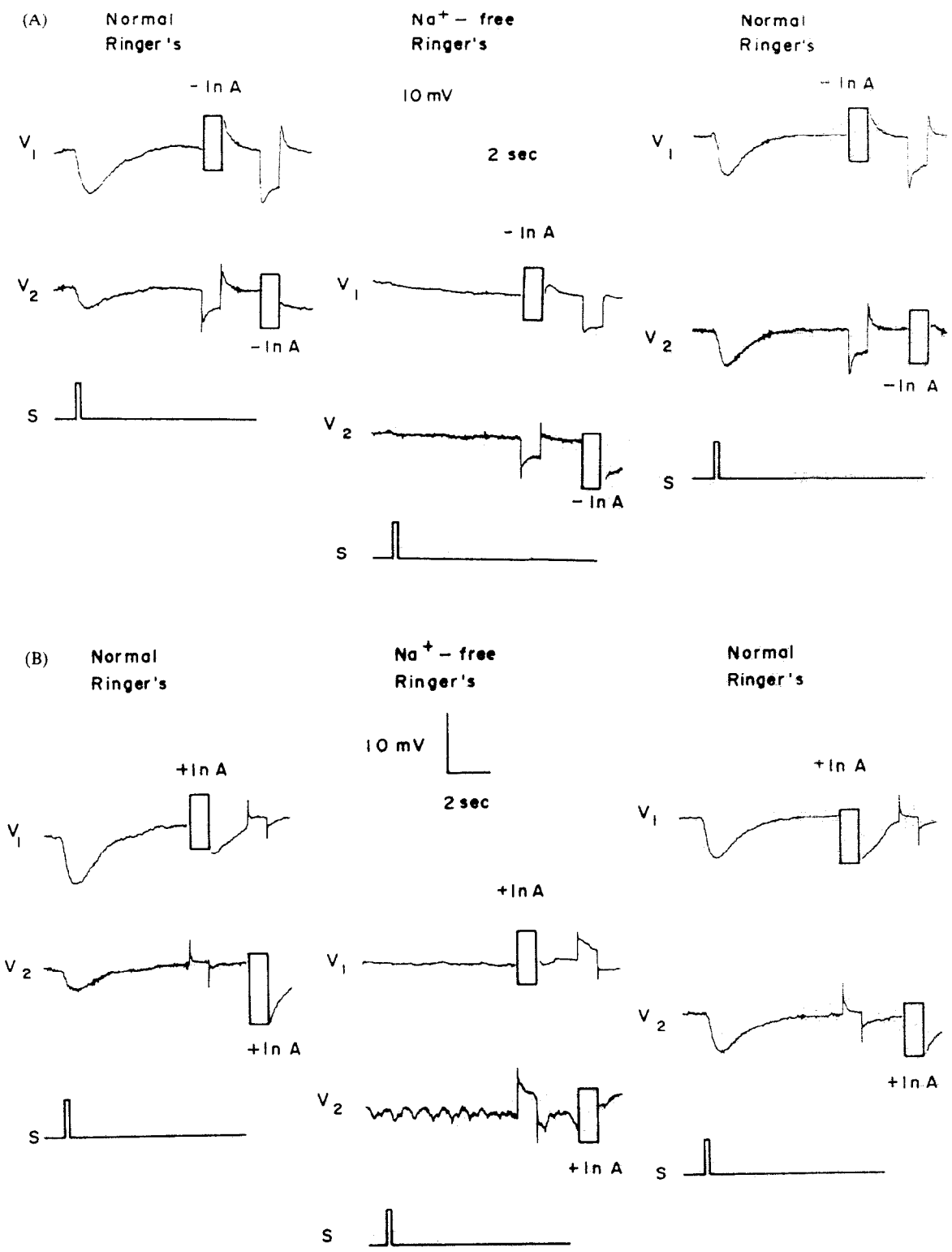

Fig. 2. Current-induced potentials in Na^+-free Ringer's. Two rods were simultaneously impaled and their membrane potentials monitored as shown by traces V_1 and V_2; 200 msec stimuli were delivered as indicated by trace S. When the preparation was superfused with Na^+-free Ringer's (Solution A, center column), the membrane potentials of both rods hyperpolarized (shown by the displacement of each trace) and the responses to light were abolished. (A) Hyperpolarizing current, injected into each rod as indicated by the rectangles, caused a current-induced hyperpolarization in the other rod of the pair. A change in the waveform of the current-induced potential was observed in some cells. (B) Depolarizing current, injected into each rod as indicated by the rectangles, caused a current-induced depolarization of the other rod of the pair. The amplitude of this depolarization increased in the test solution.

ever, this test solution did not cause a decrease in the amplitudes of the current-induced potentials (6 interacting pairs, see Griff, 1979, Fig. 28). Increasing $[Ca^{2+}]_0$ to 14 times normal (Solution I, Table 1) also did not reduce the current-induced potentials (8 pairs). For two of the pairs the test solution increased the amplitude of the current-induced potentials.

In the crayfish septate axon Asada and Bennett (1971) demonstrated that treatment with low $[Ca^{2+}]_0$ caused a 3-fold decrease in coupling and that upon return to normal $[Ca^{2+}]_0$ a decrease of nearly 30-fold occurred. Rose and Loewenstein (1976) demonstrated that exposure to Ca^{2+}-free medium caused uncoupling in *Chironomus* salivary glands and that the uncoupling was accompanied by an increase in $[Ca^{2+}]_i$. We therefore examined the effects of decreasing $[Ca^{2+}]_0$.

Simply lowering $[Ca^{2+}]_0$ from 0.86 to 0.21 mM (Solution D, Table 1) reduced the amplitudes of the current-induced potentials. In this test solution the rod depolarized and the input resistance decreased (Griff, 1979, Fig. 23) presumably due to an increase in Na^+-conductance of the non-junctional membrane (Brown and Pinto, 1974; Oakley and Pinto, 1980). We therefore tried to eliminate this change in non-junctional conductance by removing extracellular Na^+.

The free $[Ca^{2+}]_0$ was further reduced by buffering $[Ca^{2+}]$ to 10^{-8} M with EDTA; TMA^+ replaced Na^+, and the pH of the solution was adjusted to 7.8 with HEPES buffer, KOH, and Tris-base (Solution E, Table 1). The free $[Ca^{2+}]$, measured with a Ca^{2+}-selective microelectrode positioned above the retina, was 10^{-7} M. When this test solution was substituted for normal Ringer's, the membrane potentials of two simultaneously impaled rods remained constant or hyperpolarized. The amplitudes of the light responses were attenuated by 60% to 90%, and the amplitudes of the current-induced potentials became undetectable (see Fig. 5); these results were observed for 4 interacting pairs of rods. Similar results were obtained in a test solution in which EGTA was used in place of EDTA, and which contained a normal concentration of Mg^{2+} (Solution G, Table 1, 2 interacting pairs).

If the observed attenuation of the current-induced potentials in 10^{-8} M Ca^{2+}, Na^+-free test solution were due solely to uncoupling of the rods, one would expect the increase in coupling resistance to increase rod input resistance. In normal Ringer's, the mean input resistance (measured using hyperpolarizing currents) in the dark was 114 ± 51 (SD) MΩ ($N = 32$ cells). When the superfusate was switched to the test solution, the mean input resistance decreased to 67 ± 20 (SD) MΩ ($N = 20$, see Fig. 6). One explanation for the resistance changes with 10^{-8} M free Ca^{2+} and TMA^+ for Na^+ is that TMA^+ was conducted across the non-junctional membrane. Substitution of the trisaccharide raffinose for NaCl in 10^{-8} M Ca^{2+} (Solution F, Table 1), however, also caused a decrease in input resistance; for 6 cells the mean decrease was 44 ± 18 SD) MΩ.

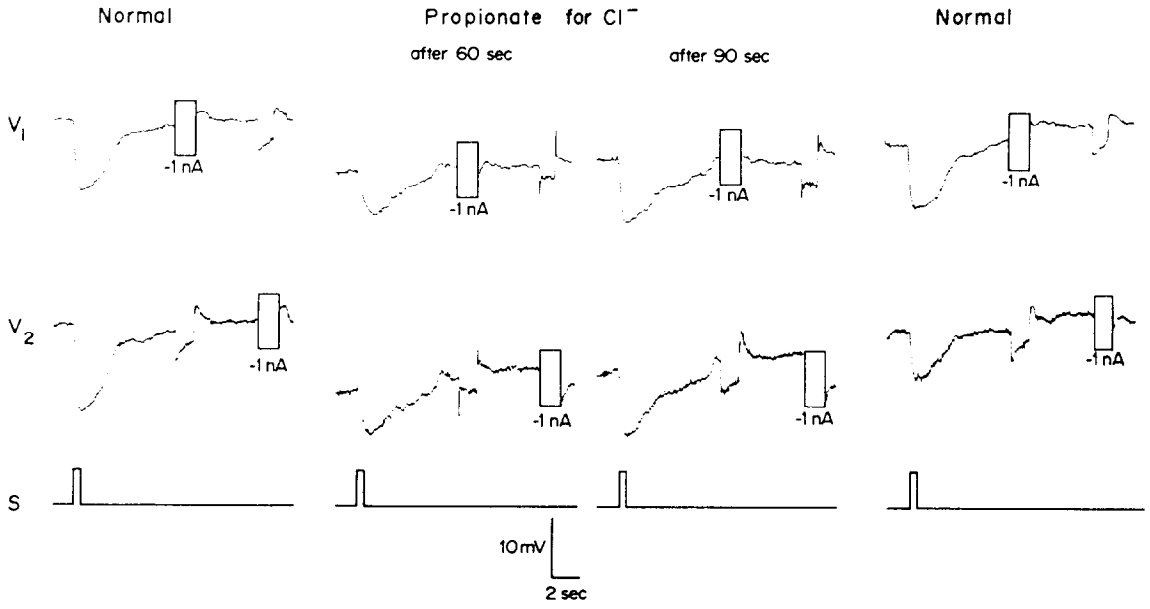

Fig. 3. The effects of low Cl^- Ringer's. Two rods were simultaneously impaled and their membrane potentials monitored as shown by traces V_1 and V_2; 200 msec stimuli were delivered as indicated by trace S. When the preparation was perfused with a solution in which Na^+-propionate replaced NaCl (center columns), the membranes of both rods hyperpolarized and the responses to light were reduced slightly. Hyperpolarizing current was injected into each rod as indicated by the rectangles. This test solution had little effect on the amplitudes of the current-induced potentials.

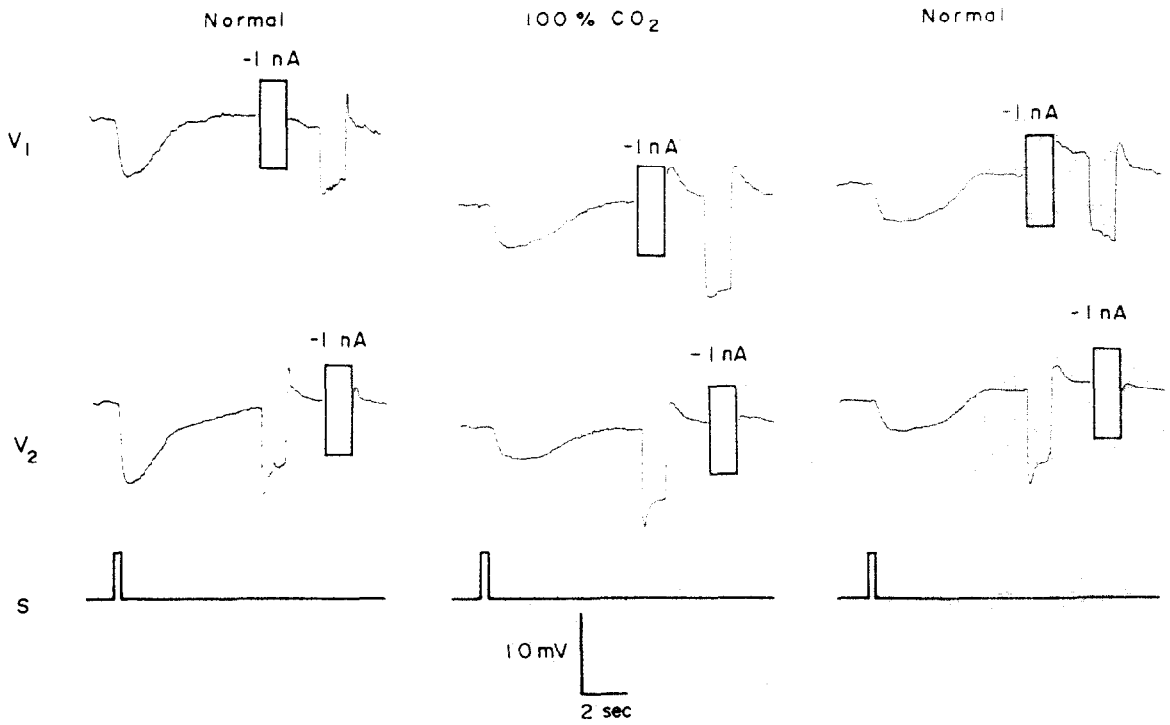

Fig. 4. The effects of decreased intracellular pH. Two rods were simultaneously impaled and their membrane potentials monitored as shown by traces V_1 and V_2; 200 msec stimuli were delivered as indicated by trace S. When the preparation was superfused with bicarbonate-buffered Ringer's that was equilibrated with 100% CO_2 (Solution B, center column), the membranes of both rods hyperpolarized and the responses to light were diminished. Hyperpolarizing current was injected into each rod as indicated by the rectangles. The test solution had little effect on the current-induced potentials.

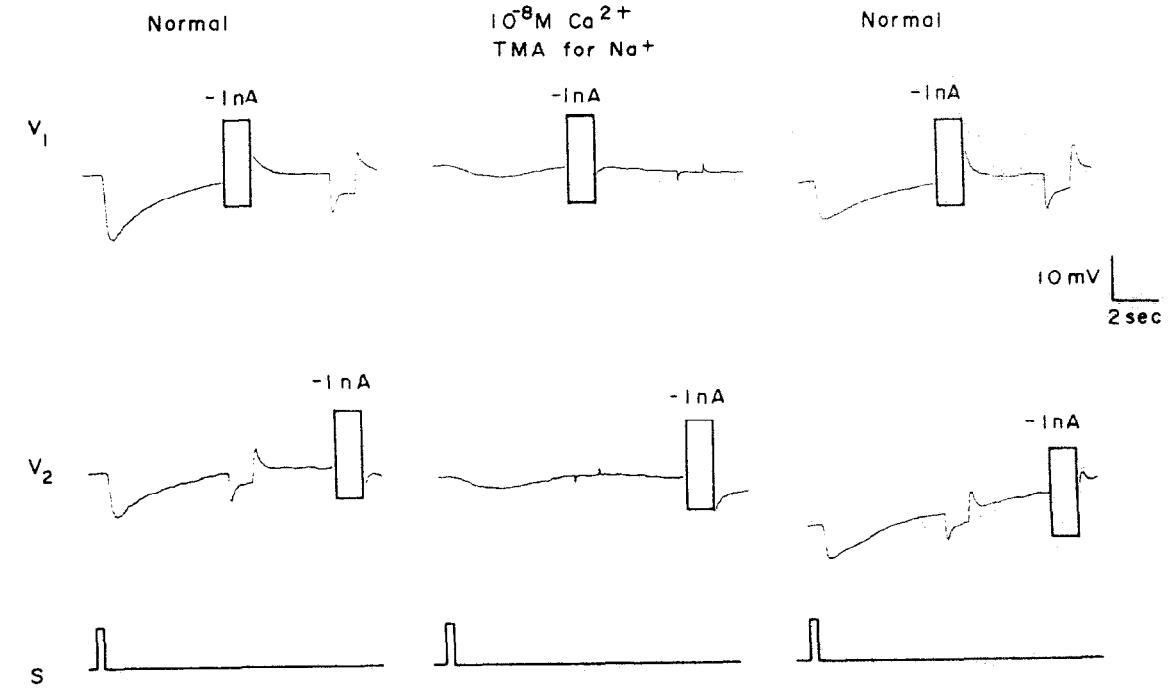

Fig. 5. The effects of Na^+-free Ringer's containing 10^{-8} M free Ca^{2+}. Two rods were simultaneously impaled and their membrane potentials monitored as shown by traces V_1 and V_2; 200 msec stimuli were delivered as indicated by trace S. When the preparation was superfused with solution (E) in which the free $[Ca^{2+}]$ was buffered to 10^{-8} M with EDTA, and tetramethylammonium (TMA) chloride was substituted for NaCl (center column), the amplitudes of the light responses were reduced at least 90%. Hyperpolarizing current was injected into each rod as indicated by the rectangles. The test solution caused the current-induced potentials to become undetectable.

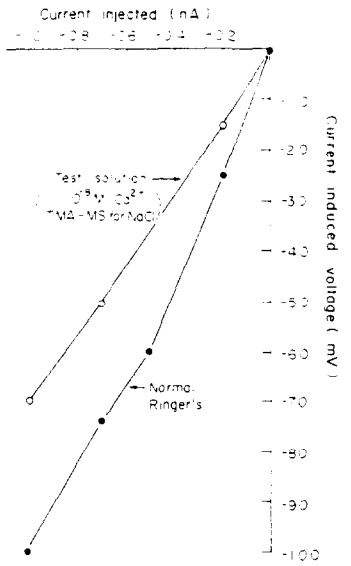

Fig. 6. Steady-state current–voltage relationship. A single rod was impaled with a double-barreled microelectrode. The voltage recorded through one barrel is plotted as a function of the current injected into the other barrel. The solid circles show the current–voltage relationship recorded in normal Ringer's; the open circles show the current–voltage relationship in test solution G in which the free $[Ca^{2+}]$ was buffered to 10^{-8} M with EGTA and in which tetramethylammonium methanesulfonate replaced NaCl.

DISCUSSION

Interpretation of Current-Induced Potentials

The spread of voltage in the rod network is a function of the junctional and non-junctional resistances (Lamb and Simon, 1976). The amplitudes of current-induced potentials recorded between two interacting rods could, therefore, be altered if either resistance changed. Studies of isolated rods have shown that the current–voltage (I–V) relationship of the rod is non-linear, rectifying strongly at potentials more positive than the dark resting potential (Bader *et al.*, 1979; Werblin, 1979; Attwell and Wilson, 1980). Current-induced potentials also rectify above the resting potential; depolarizing current produces a smaller potential than hyperpolarizing current. For potentials more negative than the dark potential, the I–V relationship is approximately linear (Fig. 6; Bader *et al.*, 1979; Werblin, 1979; Attwell and Wilson, 1980). If all rods in the network are hyperpolarized by bathing the retina in a low Na^+-Ringer's, the current-induced potentials for depolarizing and hyperpolarizing current become equal (Fig. 2). We interpret these results to indicate that a change in the bathing solution, by changing the cell's membrane voltage, can cause the cell to operate in a different region of the current–voltage relationship, and thereby alter the non-junctional resistance. This latter change in resistance can alter the amplitude of the current-induced potentials.

Another complication is that the amplitude of the current-induced potential is not a monotonic function of the junctional resistance (Detwiler and Hodgkin, 1979). If the junctional resistance between a pair of cells separated by a given distance is infinite, the cells are, of course, uncoupled, and current injected into one of the cells will induce no potential in the other. For a large, finite junctional resistance, current injected into one of the cells will induce a potential in the other cell. The magnitude of the potential will be greater for smaller junctional resistances within this range of resistance. For a certain value of junctional resistance the current-induced potential will be maximal, and lower junctional resistance will actually be accompanied by current-induced potentials of submaximal magnitude. (This phenomenon can be thought of as due to a spread of current beyond the cell whose current-induced potential is being considered.) Because of the non-monotonic dependence of current-induced potentials upon junctional resistance, our measurements can not necessarily be used to determine the effect of a test solution on junctional resistance. However, we should note that in no case did we observe the amplitudes of the current-induced potentials to vary with time in a non-monotonic fashion during a change in solution. Thus, we believe that our experiments were performed within the range of cell separation and resistance for which increased resistance would cause a decrease of current-induced potential.

Ionic dependence of rod coupling

We have examined the dependence of rod coupling on the extracellular ionic composition by studying the effects of low Na^+ and low Cl^- test solutions. Since the amplitudes of the current-induced potentials were not reduced in the Na^+-free test solution, we conclude that these potentials are not generated primarily by changes in sodium conductance. We also conclude that these potentials are not generated primarily by changes in potassium conductance, since the rod membrane hyperpolarized in Na^+-free test solution, thereby decreasing, although probably not eliminating, the driving force on K^+ (Capovilla *et al.*, 1981). If the interactions were mediated primarily by changes in potassium conductance, the current-induced potentials would have been reduced with reduced driving force.

We also conclude that the interactions are not mediated primarily by changes in chloride conductance. In a Cl^--free test solution the membrane hyperpolarized about 10 mV, suggesting that a chloride conductance might have been present in the dark (Capovilla *et al.*, 1980, but see Pinto and Ostroy, 1978). However, current-induced potentials were not reduced in the Cl^--free test solution. Thus, persistence of the interactions in Na^+-free and Cl^--free test solutions supports the hypothesis that rods interact, not by chemical synapses, but by electrotonic coupling.

Effects of treatments that cause uncoupling in other systems

We examined the effects of chemical treatments that uncouple electrotonic synapses in other systems. If rods became uncoupled, the current-induced potentials should have become undetectable and the input resistance should have increased. Surprisingly, no treatment was found that caused both of these changes in the rod network. We assume that each test solution has access to the inner segment and terminal area, since superfusion with a Ringer's containing 10^{-5} M cobalt inhibited synaptic transmission from rods to horizontal cells (Griff, 1979, Fig. 16). The only treatment that caused a drastic reduction of current-induced potentials was low Ca^{2+}, but this test solution also decreased input resistance. In a model of the rod network (Griff, 1979) we determined that a decrease in non-junctional resistance from 500 to 200 MΩ would account for both the decrease in current-induced potentials and the decrease in input resistance.

Treatment with 100% CO_2-Ringer's did not uncouple the rod network. Similar resistance to uncoupling with CO_2 treatment has also been reported for chick lens (Goodenough and Schuetz, 1980), where freeze fracture replicas of the gap junctions reveal a non-crystalline aggregation of "connexons" (Casper *et al.*, 1977) indicative of a network that would be expected to resist uncoupling (Goodenough, 1979). It is interesting that in the rod network, the "connexons" are also of the non-crystalline form (Gold and Dowling, 1979). Thus, the ultrastructural properties of the photoreceptor gap junctions may explain their resistance to uncoupling.

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