

Effects of Polarization of the Receptor Membrane and of the First Ranvier Node in a Sense Organ

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ABSTRACT It has previously been shown that the site of production of the generator potential in Pacinian corpuscles is the receptor membrane of the non-myelinated ending, and the site of initiation of the nerve impulse, the adjacent (first) Ranvier node. Effects of membrane polarization of these sites were studied in the present work. Nerve ending and first Ranvier node were isolated by dissection, electric activity was recorded from, and polarizing currents were passed through them. All observations were done at steady levels of polarization, seconds after onset of current flow. The following results were obtained:

The amount of charge transferred through the excited receptor membrane is a function of the electrical gradients across the membrane. The generator potential in response to equal mechanical stimuli increases with resting potential of the receptor membrane. The refractory state of the generator potential is not affected by polarization.

The electrical threshold for impulse firing at the first Ranvier node (measured by the minimal amplitude of generator potential which elicits a nodal impulse) is nearly minimal at normal resting potential of the node. Both, hyperpolarization and depolarization lead to a rise in nodal threshold.

For any level of polarization of nodal and receptor membrane, the threshold for production of impulses by adequate (mechanical) stimulation appears determined by the generator potential-stimulus strength relation and by the electrical threshold of the node.

INTRODUCTION

The receptor membrane of the non-myelinated nerve ending of Pacinian corpuscles has the peculiarity that small regions of it can be excited inde-

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pendently of each other. If a mechanical stimulus is applied to a small portion of ending, the resulting active electric response (depolarization) is confined to that region which has been stimulated mechanically, and does not propagate over non-stimulated regions of the same receptor membrane by local circuit excitation (17, 18). Thus, in the receptor membrane, active transfer of charge appears to be a localized process, unlike that in a membrane with regenerative responsiveness. This paper deals with the effects of electrical gradients on the charge transfer. By polarizing the receptor membrane with inward or outward currents, evidence will be given that, as in a membrane with regenerative responsiveness, charge transfer increases with the electrical gradients across the membrane.

This paper deals also with the more special question of the effects of polarizing currents on the threshold for adequate (mechanical) stimulation of a sense organ. Interactions between polarizing currents and the adequate stimulus have been described for several kinds of sense organs (2-4, 6-8, 10, 13-15, 21-25, 28). With the exception of the work of Diamond, Gray, and Sato (3), of MacNichol, Wagner, and Hartline (23, *cf.* reference 22), and of Fuortes (6), the action potential alone, rather than the generator potential, has been used as an index for changes in responsiveness and rhythmicity. The decapsulated preparation of Pacinian corpuscles (20) used in the present experiments, in which the receptor membrane and the first Ranvier node are partially denuded, offered the opportunity to analyze the effects of polarizing currents on the threshold for adequate stimulation in terms of the generator potential of the receptor membrane and the electric threshold of the first Ranvier node inside the sense organ. The sites of origin of electrical activity in Pacinian corpuscles are known: the generator potential arises at the non-myelinated ending, and the all-or-nothing potential, at the first Ranvier node inside the corpuscle (20). In the decapsulated preparation these sites are partially isolated; electrical activity can be directly recorded from, and currents can be directly applied to these sites. It will be shown by this procedure that the mechanical threshold of the sense organ is markedly changed when polarizing currents are passed through the ending and node; and that these changes can be explained in terms of changes in generator potential of the ending and in electrical firing threshold of the first Ranvier node.

A preliminary note on these results has appeared elsewhere (13).

Methods

Pacinian corpuscles of the cat's mesentery were isolated together with a length of sensory axon. They were set up in a bath containing a Krebs's solution covered with mineral oil (Fig. 1). Mechanical stimulation of the receptor was provided by an

electrically driven piezoelectric crystal (8, 19). Mechanical pulses of 1 to 2 msec. duration, and continuously variable in amplitude from 0 to 45 μ were available for stimulation. Currents from a variable d.c. source were passed through the non-myelinated ending and myelinated axon with a pair of non-polarizable AgCl-Cl electrodes. One of the electrodes consisted of a glass pipette filled with a stiff Krebs's solution-agar-jelly and a AgCl-Cl wire. The axon was drawn through the jelly as shown in Fig. 1, while the latter was still setting; this insured a stable contact after the setting of the jelly. Contact between the axon and the other AgCl-Cl electrode was made through the Krebs's solution; the effective electrode was the oil-Krebs's

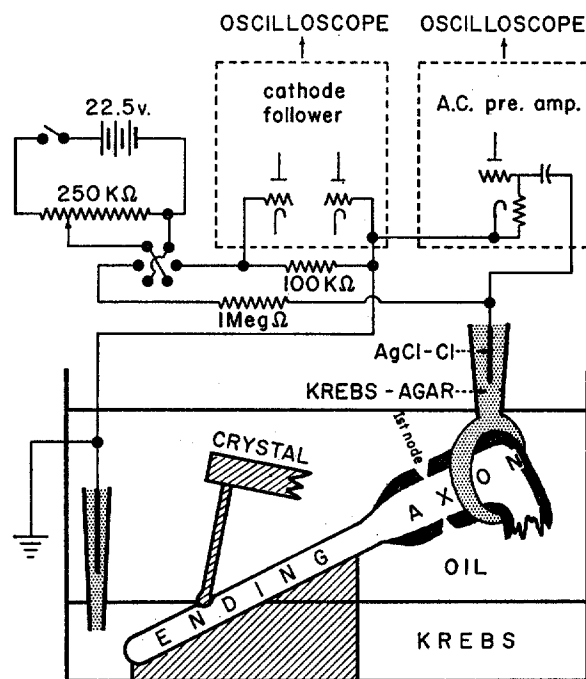


FIGURE 1. Diagram of set-up. Description in the text.

solution-interface. In the experiments with intact corpuscles the interface was adjusted to be at the point of axon emergence from the corpuscle; in the experiments with decapsulated corpuscles, the interface was made to lie either at the non-myelinated ending or at the first node of Ranvier. These electrodes were used at the same time for the recording of electrical activity from the receptor. The electrical activity was fed through a capacity-coupled preamplifier into one beam of a double beam oscilloscope. The other beam was used for recording of the polarizing current. The stimulating pulses of the crystal were monitored photoelectrically on another oscilloscope. The technique for capsule removal from Pacinian corpuscles has been described elsewhere (20). The experiments were done at room temperature ranging between 20 and 26°C.

RESULTS

Effects of Polarizing Currents on Generator Potential

When mechanical stimuli of equal strength and duration are applied to a Pacinian corpuscle, generator potentials of rather constant amplitude and shape are produced at the non-myelinated ending inside the corpuscle. There are spontaneous fluctuations in generator potential inherent in the nature of the excitation process at the ending's receptor membrane; but under well

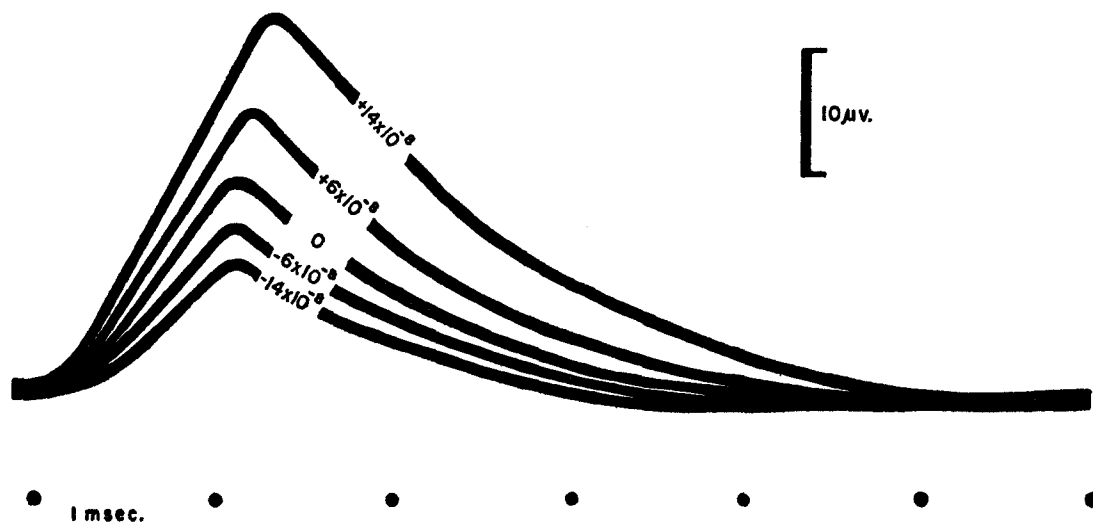


FIGURE 2. Mechanically elicited generator potentials at various levels of receptor membrane polarization. The corpuscle is stimulated with equal mechanical stimuli, while its nerve ending is being hyperpolarized or depolarized with, respectively, inward (+) or outward (−) currents. The numbers on each generator potential give the intensities in amperes of the corresponding polarizing current.

controlled conditions of constant stimulations they usually amount to less than 12 per cent (12, 19). If an inward current is passed through the non-myelinated ending, so as to increase its resting potential, the generator potential in response to a given mechanical stimulus is markedly changed: its mean amplitude and its mean rate of rise are increased. Fig. 2 illustrates these effects. Fig. 3 shows the relationship between amplitude of generator potential and polarizing current. The amplitude is seen to vary nearly linearly over a wide range of current intensity. The rate of rise is found to vary in a similar manner (Fig. 4).

The amplitude of the generator potential can be increased or decreased without detectable steps by increasing or decreasing progressively the stimulus

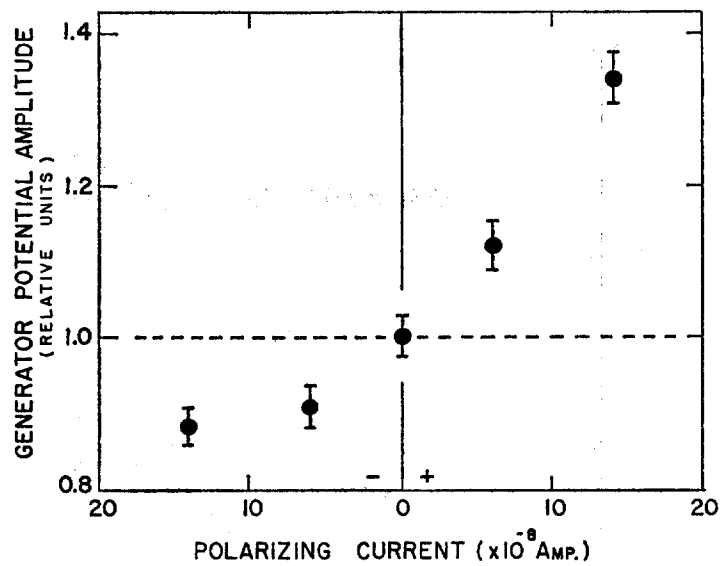


FIGURE 3. Amplitude of generator potential as a function of polarizing current. The mean amplitude of generator potential in response to equal mechanical stimuli is determined for various intensities of constant current flowing inward (hyperpolarizing) or outward (depolarizing) across the ending. In this and subsequent graphs inward flow of current is denoted by + and outward flow by -; generator potential ordinates are multiples of generator potential at resting membrane potential; and the vertical bars subtend the standard error of the mean of 50 generator potentials.

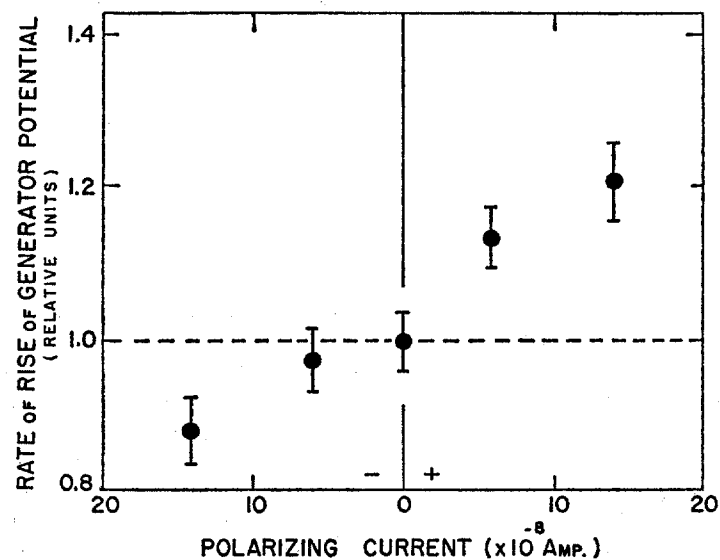


FIGURE 4. Rate of rise of generator potential as a function of polarizing current. The average rate of rise of generator potential whose amplitude was plotted in Fig. 3 is plotted here against the same abscissae.

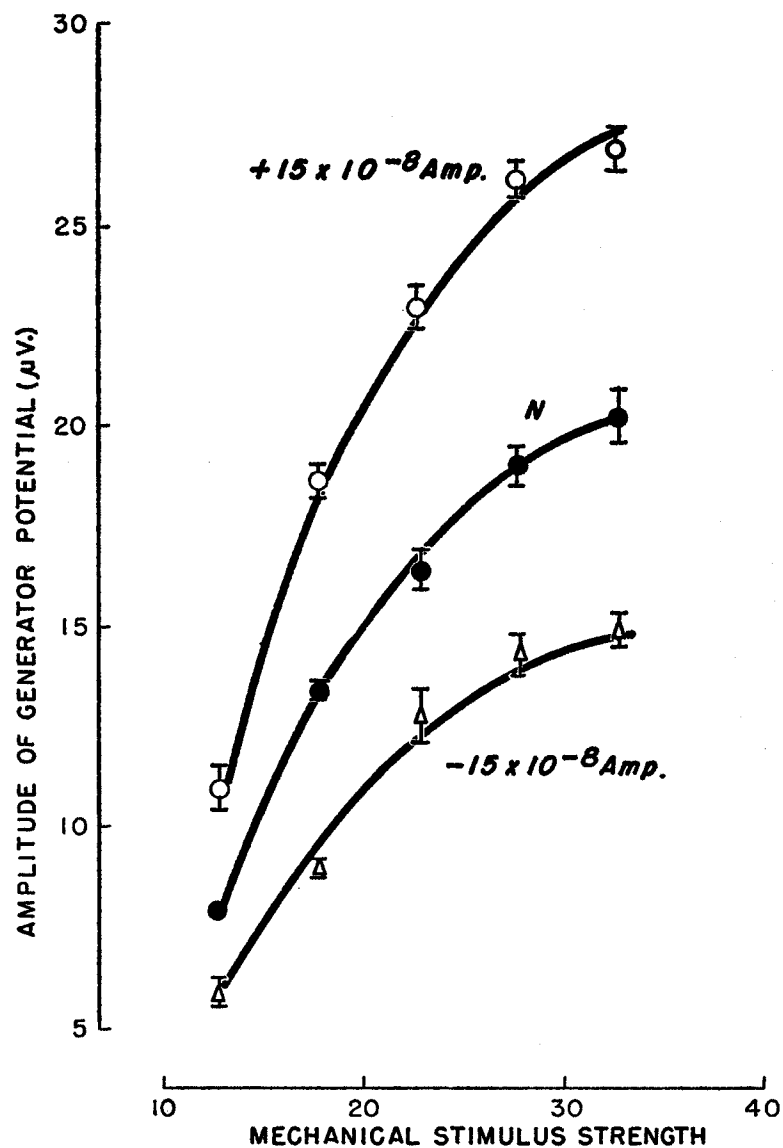


FIGURE 5. The transducer relation of the receptor membrane at various levels of polarization. The generator potential-stimulus strength function is determined in the receptor membrane at normal resting potential (●); in the receptor membrane depolarized (Δ) by a constant outward current; and hyperpolarized (O) by a constant inward current of 15×10^{-8} amp. The values of generator potential obtained in the depolarized and hyperpolarized membrane fall on curves which respectively multiply the corresponding normal generator potential curve by factors of 0.73 and 1.35.

strength (1, 9). Over a certain range of stimulus strength the amplitude of the generator potential is a nearly linear function of stimulus strength; *i.e.*, of the amplitude of mechanical pulses of the crystal stimulator. We have studied the generator potential-stimulus strength relationship at various levels of membrane polarization within this nearly linear range. Fig. 5 shows a family of curves obtained at three levels of polarization in a typical ending. Polarization is found to multiply the generator potential at any given stimulus strength by a constant factor.

In all experiments of the present paper, changes in generator potential due to polarizing currents were determined with the polarizing current at a constant intensity. Changes in generator potential were recorded only after the corresponding polarizing current had been on for at least 30 sec. This applies also to the measurements of changes in nodal action potential and firing threshold described below. Stable conditions were thus ensured.

Effects of Polarizing Currents on the Action Potential of the First Ranvier Node

EFFECTS ON NODAL ACTION POTENTIAL When the generator potential reaches a certain critical amplitude, an all-or-nothing potential is discharged inside the corpuscle which propagates along the myelinated axon of the corpuscle. Generator potential and all-or-nothing potential are produced at anatomically and functionally distinctly different membrane sites: the generator potential is set up at the non-myelinated ending, a structure apparently incapable of producing regenerative responses; and the all-or-nothing potential arises at the first Ranvier node inside the corpuscle, a structure with typical regenerative responsiveness (20). Ending and node are separated by a cylinder of myelin of about 250 μ length. The preparation offers thus the opportunity to study the effects of polarizing currents on a structure with regenerative mechanisms side by side with one which lacks such mechanisms.

Fig. 6 shows the all-or-nothing potential of the first Ranvier node as obtained at three different levels of polarization. The action potential was produced by applying suprathreshold mechanical stimuli of equal strength and duration to the non-myelinated ending, while constant inward or outward currents of various intensities were passed through the node. As in other structures with all-or-nothing responsiveness, the amplitude of the action potential increases and that of its positive after-potential decreases as a function of inward current; and with outward currents, the action potential decreases and the positive after-potential increases (Fig. 6). The rate of rise of the nodal action potential is seen to increase with inward and to decrease with outward current, but the change in rate of rise per unit change of

polarizing current is smaller than that of the generator potential at any corresponding current intensity, in spite of the density of polarizing current at the node being almost certainly higher than at the ending.

EFFECTS ON NODAL FIRING THRESHOLD The minimal outward current which must flow through the first node in order to fire an all-or-nothing potential, *i.e.* in order to reduce the nodal membrane potential to the critical

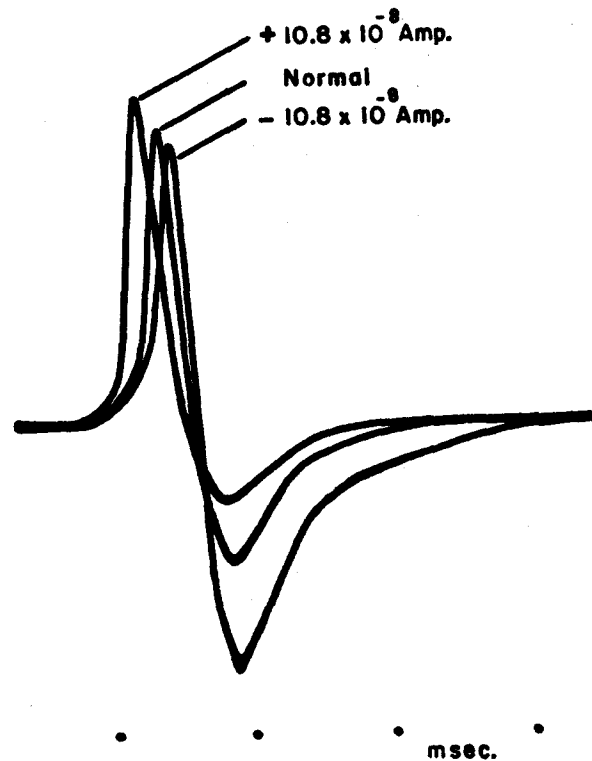


FIGURE 6. Action potential of the first Ranvier node of the sense organ at various levels of nodal polarization.

firing level, is rather constant (9, 19). The transducer structure of the non-myelinated ending provides a built-in current sink for the adjacent node; the current intensity of this sink can be readily varied over an ample range by adjusting the strength of mechanical stimuli. Since the external resistance, namely that of the capsular tissue and fluid around ending and node may be regarded as a constant, the generator potential as recorded with the present method gives a measure of the current flow between ending and node. The minimal generator potential which triggers the all-or-nothing potential at the node will henceforth be referred to as *nodal firing threshold*. The following procedure was used for determination of the nodal firing threshold: the

strength of mechanical stimuli was so adjusted as to cause generator potentials of critical amplitude for all-or-nothing firing. Thus, upon repetitive stimulation with equal stimuli, some generator potentials will elicit all-or-nothing potentials, while others will abort. Five or ten successive responses were photographed on superimposed oscilloscope sweeps. The maximal amplitude of abortive generator potential was taken as a measure of the nodal firing threshold.

When a constant polarizing current is passed through the first node, changes in its firing threshold are observed (Fig. 7). Fig. 8 illustrates these changes as a function of polarizing current for two typical corpuscles. Constant inward or

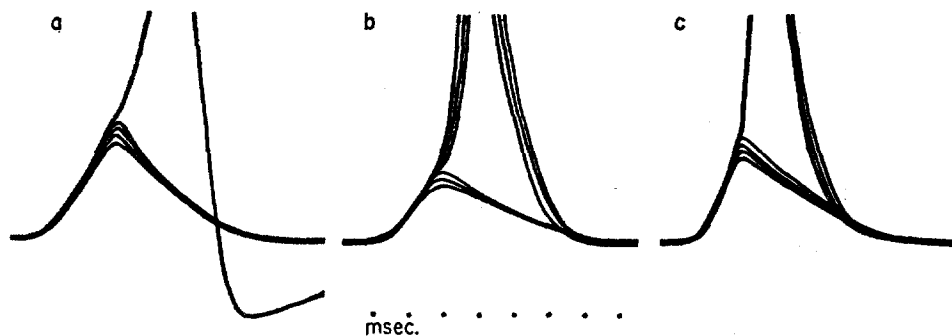


FIGURE 7. Changes in electrical threshold of the first Ranvier node of the sense organ under the influence of polarizing currents. The corpuscle is stimulated with mechanical stimuli adjusted to cause generator potentials critically at threshold for impulse firing while *a*, a constant outward (depolarizing) current of 0.25×10^{-6} amp.; *c*, and an inward (hyperpolarizing) current of 1.5×10^{-6} amp. are passed through the first Ranvier node. *b*, normal firing threshold at 0 current.

outward currents were passed through the node, while the nodal firing threshold was tested with mechanically elicited generator potentials. Starting from a certain current intensity, the firing threshold is found to increase above normal with increasing inward current. With outward currents the firing threshold also increases. The curve of Fig. 8 resembles in its general shape Tasaki's (27) threshold curves for Ranvier nodes of frog motor nerves. The increase in firing threshold with *inward* currents (which will expectedly increase the nodal resting potential) was certainly to be expected. The increase in threshold with *outward* currents reveals once more that the first Ranvier node of Pacinian corpuscles is rapidly inactivated when subjected to constant outward currents. Earlier experiments had already shown that the first Ranvier node of Pacinian corpuscles is rapidly inactivated under the influence of a constant generator current from the ending flowing through the node: when a generator potential is built up and maintained continuously by repetitive stimulation, no all-or-nothing potentials can be elicited from

the node while this constant generator current is flowing between node and ending (16). It seems likely that the present result on the nodal threshold, caused by a constant outward current whose sink is at the axon under the positive polarizing electrode, and the earlier result, caused by a constant outward current with a sink at the excited receptor membrane of the ending, are both caused by an inactivation process (*cf.* reference 11) at the first

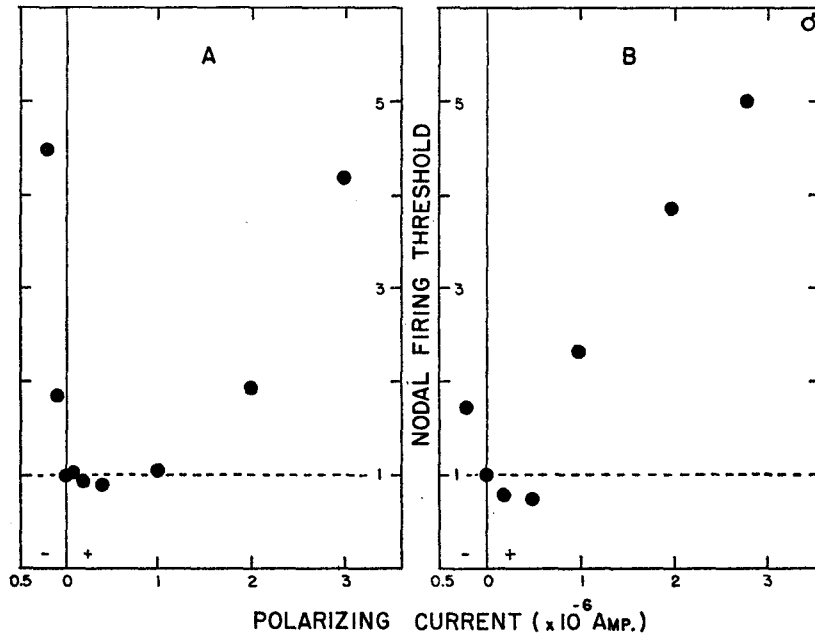


FIGURE 8. The electrical threshold of the first Ranvier node as a function of polarizing current. The nodal firing threshold is determined for a range of constant polarizing currents flowing inward or outward through the first Ranvier node of the sense organ. *A*, data from a corpuscle with intact capsule in which polarizing currents were applied to, and electrical activity was recorded from the point of axon emergence from the corpuscle; that is, at about 100μ distance from the first node. *B*, data from a decapsulated corpuscle in which current was applied to, and electrical activity recorded directly from the first Ranvier node. Ordinates, multiples of normal nodal firing threshold.

Ranvier node. A rather unexpected finding was the decrease in nodal firing threshold in the low range of inward current (Fig. 8 *B*). This effect was observed in six out of ten corpuscles. In four corpuscles the effect was not clearly seen; the firing threshold appeared then to be not significantly changed from that at zero polarizing current in the low range of outward current (Fig. 8 *A*). This latter kind of behavior requires no further explanation; it is the result which one might expect if hyperpolarization were the only factor involved in determining the increase in nodal threshold. However, decrease in nodal firing threshold in the low range of inward current was the more commonly

observed behavior. The effect could be explained if the first Ranvier node were to be partially inactivated under the present resting conditions. Weak inward currents may then counteract the inactivation and bring about a lowering of threshold as observed. It is difficult to ascertain what the source is for this inactivation. The possibility that the node may be inactivated by a constant injury current flowing outward through the first node to a sink located at the crushed portion of axon, is unlikely: assuming a nodal transmembrane resistance of 100 meg Ω and certain other membrane constants (18, 26), the injury current through the first node can be estimated to be of the order of 10^{-11} amp. if the crushed region lies about twelve nodes distant from the first node. This current is three orders of magnitude too low to account for the observed change in threshold. A more likely explanation of nodal inactivation may be given by assuming that in the isolated corpuscle, the first Ranvier node is slightly depolarized under resting conditions by leakage of K^+ or other ions through the nodal membrane.

In Fig. 8 *B* the nodal firing threshold is seen to decrease frankly below normal, while in 8 *A* the threshold remains approximately normal in the low range of inward current. That the curves depicting the two types of threshold behavior belong respectively to an intact and a decapsulated corpuscle is fortuitous. The two types of behavior are found in Pacinian corpuscles regardless of whether they are decapsulated or not.

Direct Polarization and Recording at the Ending

Results were described in the preceding paragraphs indicating that the generator potential increases as a function of current flowing inward through the non-myelinated ending. The recording conditions in these experiments were such that the generator potential of the ending had to spread electrotonically over a stretch of about 450 μ of intracorporeular myelinated axon before reaching the recording electrode. The same stretch of axon was also in the field of inward current when polarizing currents were applied (see Methods). The possibility, therefore, existed that the transmembrane resistance and, hence, the length constant of this stretch of myelinated axon increased under the influence of inward current. An increase in length constant would, of course, work in the same direction as a hyperpolarization of the ending's membrane, determining an increase in generator potential recorded by electrotonic spread. In order to eliminate possible contributions to the recorded increase in generator potential by changes in length constant, we have recorded directly from the ending in three corpuscles. The non-nervous capsular tissue of these corpuscles was removed by dissection so as to free the intracorporeular myelinated axon and parts of the non-myelinated ending. As has been shown in earlier experiments, such a preparation consisting

essentially of a nerve ending and a piece of myelinated axon continues to be as mechano-sensitive as in the normal sense organ (20). Under these conditions an electrode can be placed directly onto the ending, and the first node of Ranvier can be viewed with darkfield illumination. Generator potentials were thus led off directly from the ending, while at the same time polarizing currents were passed directly through it with the same electrodes (Fig. 1). The generator potential was found to vary as a function of polarizing

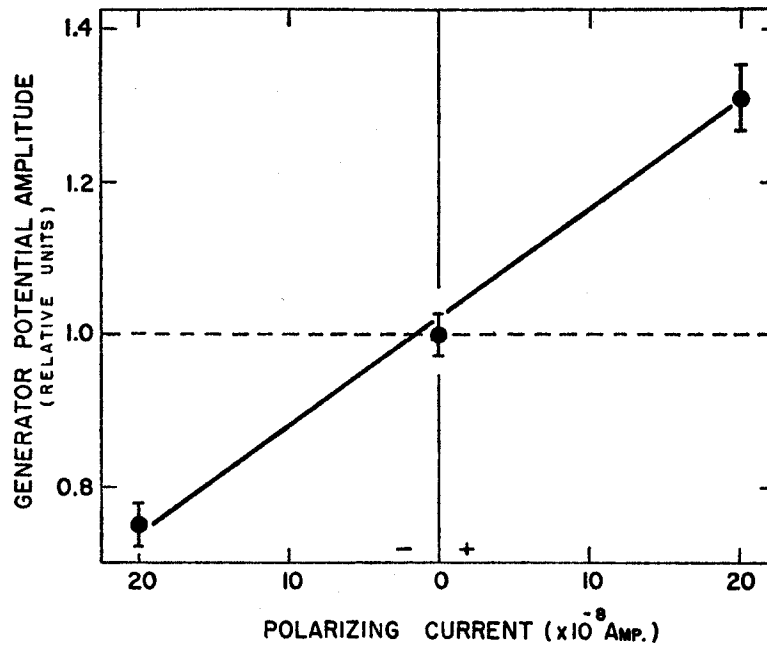


FIGURE 9. Generator potential in response to equal mechanical stimuli as a function of polarizing current as recorded directly from the receptor membrane of the non-myelinated nerve ending (decapsulated preparation).

current in essentially the same manner as already described for the intact corpuscle (Fig. 9). Controls of measurement of nodal firing threshold were also made in a few decapsulated preparations. One electrode was then placed onto the first Ranvier node for recording and polarization. Essentially the same changes in nodal firing threshold as those described for intact corpuscles were obtained (see Fig. 8).

Effects of Polarizing Currents on the Threshold for Adequate (Mechanical) Stimulation of the Sense Organ

Fig. 10 illustrates a typical experimental curve of mechanical threshold obtained in a preparation in which currents were passed through ending and

node. Such a curve is clearly to be expected from the preceding results. The threshold for the production of nerve impulses by mechanical stimulation (*mechanical threshold*) is determined by the transducer relation between mechanical stimulus and generator potential, namely the generator potential-stimulus strength function, and by the electrical threshold of the first Ranvier node. It has been seen in the preceding experiment that the generator potential decreases with rising strength of outward currents (Figs. 3 and 9). As the

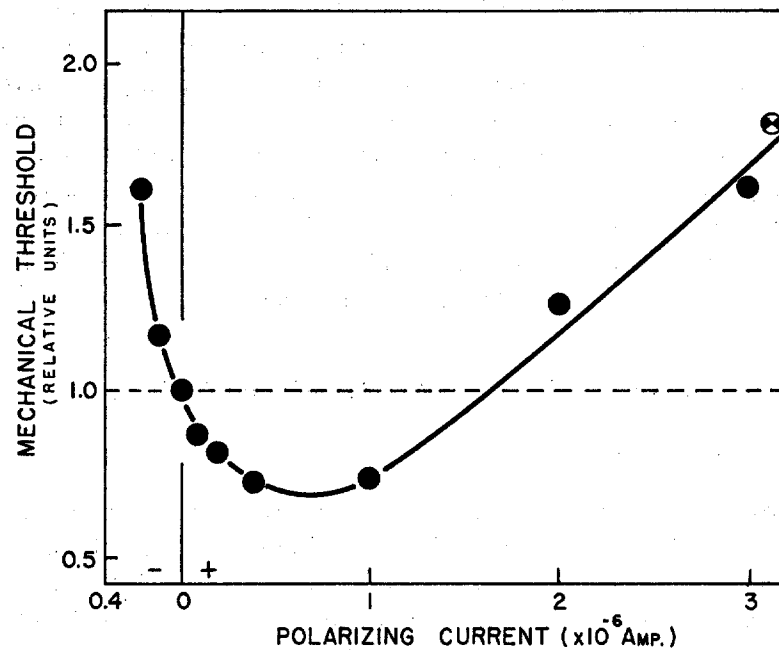


FIGURE 10. The threshold for adequate (mechanical) stimulation of the sense organ as a function of polarizing current. The minimal strength of mechanical stimulus applied to the receptor which produces all-or-nothing potentials (mechanical threshold) is measured while constant inward or outward currents of varying strengths are passed through the first Ranvier node and non-myelinated ending. Ordinates are multiples of normal threshold strength.

current is raised, the strength of mechanical stimuli must, therefore, be progressively increased in order to produce generator potentials which satisfy the electrical threshold of the node. In addition, it was found that the electrical threshold of the node increases with outward current (Fig. 8). Both effects will therefore concur in determining a sharp rise of mechanical threshold when constant outward currents are passed through ending and node (Fig. 10). With inward currents on the other hand, the generator potential increases (Figs. 3 and 9); and with low inward currents (of the order of 10^{-7} amp.) the nodal threshold remains either constant or decreases (Fig. 8 A and B). Hence a reduction in mechanical threshold will ensue when inward

currents of the order of 10^{-7} amp. are passed through the first node and ending. In the higher range of inward current the generator potential continues to rise with current intensity (Fig. 3), but at the same time the nodal threshold also rises (Fig. 8). If in this range no factor other than the nodal resting potential is involved in determining the nodal firing threshold, the mechanical threshold will depend on the relative change in resting potential at the first Ranvier node and ending (see also Discussion), which in turn will depend on the relative densities of inward current at these sites. Under the present experimental conditions, the density of polarizing current is almost certainly higher at the node than at the more distant ending. One may expect, therefore, the membrane potential at the node to increase more steeply with inward current than that at the ending and, hence, the mechanical threshold to rise with increasing inward currents. The fact is that the mechanical threshold rises in the higher range of inward current (Fig. 10). This confirms the results of Diamond, Gray, and Sato (3) who found an increase in mechanical threshold with anodal polarization of the intact corpuscle.

Polarization of the Receptor Membrane and the Refractory State

The production of a generator potential leaves a refractory condition in the receptor membrane. If two mechanical stimuli are applied successively so that the second stimulus falls on the refractory trail of the first generator response, the amplitude of the second generator potential is directly related to the stimulus interval and inversely to the strength of the first stimulus (9, 19). In the following experiments the effect of the resting potential on the refractory state was studied.

A mechanical test stimulus (S_2) of a given strength was applied to the receptor and the amplitude (G_2^0) of the resulting generator potential was measured. A conditioning stimulus (S_1) was then applied 2.3 msec. before S_2 ; the amplitude (G_2) of the test generator potential was thereby clearly reduced below its unconditioned value (G_2^0). The ratio G_2^0/G_2 was then determined at three different levels of resting membrane potential by polarizing the receptor membrane with steady inward and outward currents. Fig. 11 illustrates an experiment in which this procedure was repeated for three different values of S_1 . In all cases G_2 was found merely to vary with membrane polarization in the same proportion as G_2^0 . The polarizing currents used, caused G_2^0 to vary over a range of 75 to 140 per cent of its normal value and, consequently, may be expected to have caused the resting membrane

potential to vary over a considerable range. We may therefore conclude that, within a wide range, the refractory state of the receptor membrane is independent of resting potential.

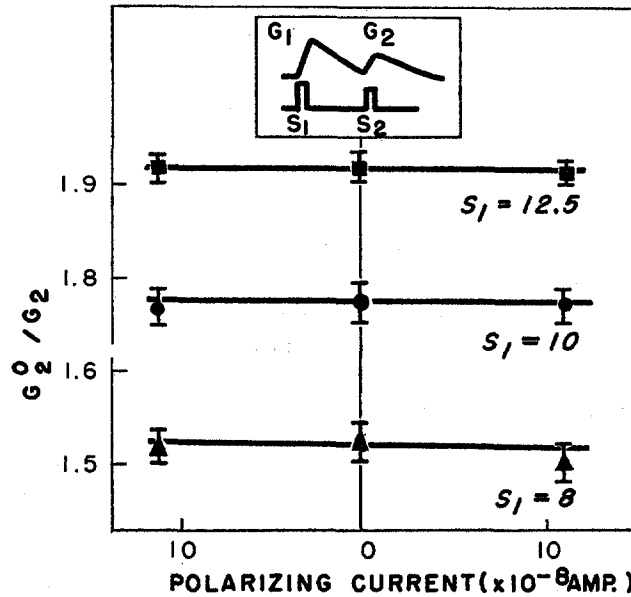


FIGURE 11. Refractory state of generator potential unrelated to receptor membrane polarization. The ratio unconditioned (G_2^0) to conditioned test generator potential (G_2) is determined for a given conditioning stimulus strength (S_1) at three levels of membrane polarization. Each point represents the mean of fifty determinations; curves drawn by least squaring (values of S_1 are displacement amplitudes (μ) of stimulating crystal).

DISCUSSION

The present results reveal that charge transfer elicited by mechanical stimulation of the receptor membrane is a function of the electrical gradients across that membrane. It is thus clear that whatever the mechanisms of mechano-electric conversion may be, the generator potential at any given active locus of the receptor membrane is not due to an invariant amount of charges as in certain piezoelectric structures.

A plausible way to explain the charge transfer is to assume that the receptor membrane of the non-myelinated nerve ending separates two media of different ionic concentrations, and that the mechanical stimulus elicits an increase in membrane conductance for one or several species of ions. If the ionic distribution is in general similar to that of other excitable nerve membranes, such a conductance change would be expected to result in a depolarizing transfer of charge through the mechanically activated receptor membrane

by ions moving along their electrochemical gradients. On this basis one would expect the charge transfer to increase with resting membrane potential. The relationship between generator potential and polarizing current described in the preceding results is in general consistent with this explanation. The fact that, unlike the case of a membrane with regenerative responsiveness, active charge transfer is here sharply localized, that is, confined to the membrane region which has been stimulated mechanically and does not spread to adjacent non-stimulated regions of the same receptor membrane (17, 18), is not expected to alter this relationship substantially (see equation below).

This peculiar type of excitation was taken into consideration in a previous paper in which an attempt was made to explain the generator potential by spatial integration of charge transfer along the receptor membrane (18). An equation was proposed to account for the generator potential-stimulus strength function in terms of area of active receptor membrane (reference 18, p. 384, Equation 1). If one replaces the numerical terms, the equation becomes

$$V = k \frac{E_m \cdot bx}{1 + bx} (1 - e^{-tR_1 C})$$

(where V is the generator potential; E_m , the resting potential across the receptor membrane; x , the ratio of active to total membrane area; $1 + b$, the ratio between resting potential and the final potential to which the membrane potential drops in the active membrane consequent to excitation by a mechanical stimulus of unlimited strength; R_1 , the parallel combination of (distributed) transmembrane resistance of the entire receptor membrane in parallel with that of active membrane; C , the lumped capacitance of the entire membrane, and k a constant whose value depends on the location of the recording electrodes). It is evident from the equation that also with this mode of excitation the generator potential would be a linear function of the resting membrane potential E_m .

It is possible that, as in certain postsynaptic structures (5, 9a, 2a), the generator potential is directly proportional to a range of resting potential. But we have never observed a reversal of polarity in generator potential in the depolarized receptor membrane. However, it is quite possible that the resting potential was not driven to a sufficiently low level in our experiments, because we were forced to limit the polarizing current to intensities of the order of 10^{-6} and often to 10^{-7} amps. At higher intensities mechanical stimulation of the preparation produced troublesome microphonic artefacts.

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