

results when the protein intake is 24 per cent is any higher than the level of calcium which gives the best results when the protein intake is 14 per cent. The present studies seem to indicate that the most beneficial level of calcium intake when the protein intake is liberal lies in the range of 0.4–0.6 per cent, or two to three times the level of minimal adequacy. In earlier studies,⁸ where calcium alone was added to Diet A, the level of optimum intake appeared to be at least three, and perhaps as much as four, times the level of minimal adequacy.

Finally, it would seem justifiable to conclude that a diet liberal both in calcium and in protein is clearly superior to a diet liberal only in protein.

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† Deceased October 7, 1955.

¹ A comparison will soon be published of the life-histories of such late-generation Diet A animals with those of their ancestors whose families had been on the diet only about half as many generations and with those of their early forebears whose families had only recently been transferred to the diet.

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MEASUREMENT OF IMPOSED VOLTAGE GRADIENT ADEQUATE TO MODULATE NEURONAL FIRING*

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Many authors^{1–31} have described the effects of polarization by imposed electric current upon nerve cells. We have not seen in the literature, however, a quantitative evaluation of the sensitivity of nerve cells to electric fields in terms of voltage gradient across some appropriate dimension of the neuron. We have undertaken to estimate the threshold value as being the unique value of greatest interest and have found this to be far lower for modulation of the frequency of an already active neuron than for the excitation of a silent one.

In selecting the measurement to be preferred for evaluating such an electric field, the estimation of voltage drop across some chosen region is a second choice to the estimation of current density through a known strategic membrane; but since we do not know how to measure the latter, we are forced to this choice. Furthermore, the selection of structures across which to measure voltage drop presents difficulties. At first glance it may appear that the structure of choice would be the cell membrane and that the inside-outside potential should be the most significant one to measure before and during threshold polarization. Upon further consideration, however, it will be realized that there will be no characteristic value for this membrane potential change, since in an equatorial region of the cell, with respect to the axis of polarization, the potential across the membrane will not be changed at all during polarization, and on one side of this line it will be increased and on the other side decreased. It will be shown, moreover, that the maximal values to be expected near the poles will be virtually beyond the limits of the sensitivity of the high impedance electrode wide-band amplifier systems we have used.

As an approximation, therefore, since we must measure the potential between two points rather than between the whole dendritic surface and the axon hillock, for example, we have measured the gradient across the whole soma in the external field, in an axis of polarization shown experimentally to be the most effective.

MATERIALS AND METHODS

The requirements for a suitable preparation for the above measurement are as follows. An accessible neuron, whose activity can be followed continuously with assurance that this activity originates in the cell under measurement, must be active at a steady level, so that alteration of its frequency by the experimental condition will be noticeable. In addition, we must be able to exclude the possibility that the effects obtained are exerted through presynaptic alterations in other neurons. An ideal preparation which satisfies these conditions is the nonadapting stretch receptor of Crustacea, described by Alexandrowicz³² and studied physiologically by Wiersma, Furshpan, and Florey,³³ Kuffler,³⁴ and Eyzaguirre and Kuffler.³⁵⁻³⁷ This is a sensory neuron whose cell body lies in the periphery, close to a special muscle fiber bundle (Florey and Florey³⁸) to which it is connected by several dendrites emerging from one side, while from the other side of the soma an axon takes origin to run to the central nervous system. Under steady stretch, this cell maintains a steady discharge of impulses at a certain frequency, and this discharge is highly rhythmic, so that very small alterations in its frequency are conspicuous.

We have used the abdominal receptors in the crayfish (*Cambarus clarkii*). These were prepared under a microscope, and the muscle bundle of the nonadapting receptor only was mounted in a device similar to that described by Eyzaguirre and Kuffler.³⁵ The companion receptor, which is a thicker-fibered and adapting one, was usually cut off. The isolated preparation was suspended in a plastic box permitting dark-field illumination and was so positioned that the soma, dendrites, and muscle bundle were in a saline solution (Van Harreveld³⁹), with the sensory axon rising into a layer of mineral oil, where recording electrodes picked up the discharge of impulses. Polarizing currents were applied through Ag-AgCl electrodes in contact with the preparation in different positions. In one series of experiments a

device was used which consisted of bar polarizing electrodes maintained at a constant separation and so mounted as to permit rotation with respect to the preparation (suspended from the paired forceps and recording electrodes). These bar electrodes were 1.5 cm. long and 2.5 cm. apart and provided in the central region occupied by the preparation a uniform field in one plane.

The voltage gradient was measured by micropipettes filled with 3 *M* KCl placed close to the cell at opposite sides in the plane of polarization. The cell is typically 40–60 μ long in the axono-dendritic axis, and the electrodes were typically not closer than 10 μ to the cell, no attempt being made to place them exactly in contact with the cell surface. Their tips could be seen, and the distance between them measured with a micrometer. A push-pull cathode follower input was used in conjunction with a Grass P-6/DC amplifier. This, together with a Dumont Type 322 cathode-ray oscilloscope, provided maximal amplification of 1 millivolt per inch. The nerve impulses led from the axon were monitored through a separate condenser-coupled amplifier. A galvanometer in series with the polarizing circuit measured the intensity of the imposed current, supplied by a battery and regulated with a potentiometer.

A second preparation used was the cardiac ganglion of the lobster (*Panulirus interruptus*). The ganglion was isolated completely, except for the posterior attachments to the myocardium, by which it remained suspended across a hole dissected in the myocardium. The preparation was immersed in mineral oil. The polarizing electrodes were applied to the anterior and posterior ends of the ganglion, and a pair of silver wires placed in the middle of the ganglion, separated longitudinally in the axis of polarization, provided both monitoring of the spontaneous rhythmic electrical discharge of the ganglion cells and recording of the voltage drop during the imposed polarization. The distance between these electrodes was measured with the ocular micrometer. This ganglion contains only five large neurons and four small ones (Alexandrowicz,⁴⁰ Maynard,^{41, 42} Hagiwara and Bullock^{43, 44}). In this case we could not place the electrodes with reference to a certain ganglion cell whose activity was identified, and we could not be sure that our estimate of threshold was the most sensitive or that the effect seen was not exerted over some small distance in the neuropile.

RESULTS

Comparative Effects of Imposed Current on Active and Inactive Neurons.—Both slow- and fast-adapting receptors, isolated from the same segment of the crayfish, were used in these experiments, and the preparations were completely immersed in mineral oil. A continuous stretch was applied to the muscle fibers, such that the nonadapting receptor was rhythmically firing between 5 and 15 impulses per second, while the adapting receptor was silent but was easily made to fire by a small increase in stretch. Polarizing electrodes were applied, one on the muscle bundles and the second on the afferent nerve close to the cell bodies. In this condition 3.6×10^{-8} ampere was sufficient to change the frequency of firing of the non-adapting receptor by 5–10 per cent. A current of $6\text{--}6.5 \times 10^{-8}$ ampere changed the frequency about 35 per cent, and $1\text{--}1.2 \times 10^{-7}$ ampere sufficed to alter the frequency 65–72 per cent. None of these currents induced the adapting receptor to discharge. Increasing the current to more than 20 times the threshold value for

acceleration of the already active neuron was still not sufficient to excite the inactive neuron. But still stronger currents did produce transient bursts therein. The directions of polarization to produce inhibition and acceleration were respectively cathode and anode on the nerve.

Voltage Gradient across the Soma Adequate To Modulate Frequency of an Already Active Neuron.—Using the nonadapting receptor immersed in saline, the voltage gradients measured between two microelectrodes placed close to the origin of the axon and close to the muscle bundle, respectively, in the axis of polarization, were in the most favorable cases 0.08–0.12 millivolt for effects between 5 and 25 per cent; 0.15–0.2 millivolt for effects of about 30 per cent; 0.2–0.4 millivolt for effects of more than 100 per cent (in the case of inhibition, a complete inhibition followed by rebound). These cells were *ca.* 60–80 μ in this dimension. The effective polarities were the same as those just given.

Preferential Axis of Polarization.—These values of voltage gradient were all obtained in the best axis of polarization of the neuron. When the field was rotated, a significant increase of the applied current was necessary in order to reproduce the same effect as that obtained in the axono-dendritic axis. At 25° of rotation, from 0 to 30 per cent more current was necessary. At 45°, from 1 $\frac{1}{4}$ up to 2 $\frac{1}{2}$ times as much current was necessary in most cases. At 90° rotation, in all experiments, the current needed to produce the same effect was from 1 $\frac{1}{4}$ up to 4 times as great. In a few cases, at 45° and 90° of rotation the polarities for acceleration and inhibition were reversed compared to those effective in the best axis. Control experiments and measurements showed that rotation did not change the threshold of current intensity by altering the position of the preparation in the field between polarizing electrodes. Changing the position of the cell without rotation did not alter the threshold current, and measuring the field showed a linear curve of voltage drop against interelectrode distance until the recording electrodes approached the polarizing electrodes within 2 mm., when a steep drop occurred.

Measurements in a Population of Neurons.—In the cardiac ganglion of the lobster, currents as low as 4.3×10^{-7} ampere are able to inhibit or accelerate by 10 per cent the frequency of the rhythmic bursts corresponding to heart beat. We did not attempt in these experiments to identify the activity of a particular one of the nine ganglion cells and measure the potential drop across it. But it may be assumed that the gradient measured between any pair of points in the ganglion separated by 100 μ will be approximately the same as between another pair of points of the same total cross-sectional area, since the impedance of the tissue is very low, and we did not encounter evidence of gross inhomogeneity in resistance. In the most favorable cases, the threshold voltage drop across 100 μ was 0.08–0.2 millivolt. The large ganglion cells are of the order of 40–60 μ in diameter of the cell body. Only the one axis of polarization was tried in this case, but the anatomy of the ganglion shows a predominance of orientation of cells in the long axis of the ganglion. The polarity, in agreement with Maynard,⁴⁵ was anterior anodale for inhibition and vice versa.

DISCUSSION

The results indicate that the output of neurons, provided that they are firing autorhythmically or presumably also if they are firing at a steady rate as a conse-

quence of a constant input, can be easily modulated in frequency by very low voltage gradients (*ca.* 0.1 mv/100 μ) measured in the external field across the whole soma, as compared to the voltage gradient necessary to stimulate a silent neuron. It will be clear in the evaluation of the values given that since they are measured across the maximum dimension, they are the maximum possible values across an effective dimension in the most effective axis of polarization. The voltage drop actually responsible for the modulation of firing frequencies can only be lower. This would be true particularly in the case in which a strategic portion of the membrane is of critical importance for the initiation of the discharge, since the value of the voltage gradient acting would be lower than that here measured in proportion to the smaller dimensions over which it acts, the total field in which the neuron lies being a relatively good conductor compared to the cell with its high-resistance membrane.

Aside from this consideration, it is obvious that even if the voltage gradient is as great as 0.1 mv/100 μ , the transmembrane potential change, resulting from the application of the polarizing current, will be smaller, something less than half of this in the maximum case. Even that value can obtain only at or near the poles of the cell, and at these two poles the effect on the resting membrane potential will be of opposite sign for a given direction of polarizing current. In the equatorial region of the cell, with respect to the axis of polarization, there will be no change in the membrane potential.

It is difficult to understand, on contemporary conventional theories of the determination of neuronal firing, how such a change in the membrane potential can influence the frequency of firing. Not only is it small, but there is in fact no change in the membrane potential of the neuron describable by a single term. Only by assuming an exceedingly critical firing level in voltage and, additionally, a limited portion of the neuron near one of the poles as being the region whose membrane potential is significant in determining firing, can the effect of the applied current be interpreted as acting through subtraction or addition from the slowly rising depolarization leading to each impulse. Of course, the critical polar region of the cell need not be a point but can be an extensive area of membrane, since the equator under consideration is not a geometrical but an electrical one and may be located at an anatomically quite polar latitude, depending on the area and the specific resistance of the membrane on each side of it. The difficulty with this hypothesis is that it requires that the very low-resistance axoplasm be at significantly different potentials in different parts of the interior of the neuron, a possibility which is certainly not excluded but for which we do not have independent evidence. Furthermore, the magnitude of the changes in steady depolarization, commonly associated with the control of firing, are of quite a different order of magnitude.⁴⁶⁻⁴⁸ The same is true of the values of both synaptic inhibitory and excitatory potentials, which are several millivolts in amplitude, while the potentials here considered must be not greater than some tens of microvolts.

An alternative hypothesis may be that the imposed currents are acting by creating or increasing an already present gradient between different portions of the cell membrane, i.e., that the critical difference is not the change in the transmembrane potential but the change in the potential between one point on the surface and another. These possibilities are not strictly alternative or mutually exclusive, and

they suggest two new or little-considered parameters of neuronal state critically significant in determining the activity of poised or already active cells over and above other conditions which alone may be quite adequate to fire the neuron, e.g., specific chemicals or strong electric currents.

The great sensitivity of neurons to small voltage differences tends to support the views already suggested to the effect that electric field actions can play a role in the determination of probability of firing of units in ganglionic masses within the central nervous system,⁴⁹⁻⁵⁶ at least in synchronizing cells,^{6, 57-65} and that currents adequate to exert an effect are physiologically available.^{7, 16, 19, 65-74}

If this is true, the considerations adduced here emphasize the significance of the morphology of the cell, since the geometric relations between the portions of the cell or dendritic membrane specially sensitive to the transmembrane changes, or the regions sensitive to difference in potential between different points on the surface with relation to the external field, acquire an overriding importance. Even more, the view here expressed emphasizes the importance of the architectural arrangements of groups of neurons and of their complex dendritic ramifications, which will be, as it were, antennae oriented with respect to the direction of currents of physiological significance to these cell masses. If this view is correct, it would be necessary to predict that in structures such as the cerebral cortex, in which orientation of many neurons is not random but characteristic, these neurons must normally be subject to physiologically significant field effects of a relatively constant axis. Since this axis is probably the most effective axis for polarization effects and since we may guess, for example in the case of the pyramidal cells of the cerebral cortex, that this will be the longitudinal axis of the cell, the expectation stated means that we would anticipate a higher voltage gradient in the extracellular fluid consequent to neuronally significant events in the axis normal to the surface than tangentially. But different axes may be simultaneously effective, as is suggested by the specific geometry of the processes in the molecular layer of the cerebellar cortex.

Finally, it may be pointed out that this view, while superficially in agreement with the theory of Gesell,^{75, 76} is significantly different in this respect: that the gradient between one part of the surface and another, which is supposed to be important in determining neuronal firing, exists only in the already active cell or, in the active cell, is sensitive to changes of a different order of magnitude. The silent cell, even when the attempt is made to poise it close to its threshold, as in the adapting stretch receptor, requires enormously more voltage gradient to be fired than the active cell does to be modulated.

SUMMARY

1. The voltage in the extracellular field across a single nerve cell has been measured with microelectrodes during polarization with imposed current just sufficient to modify the frequency of firing of an already active cell, using a preparation from the nonadapting stretch receptor of the crayfish abdomen and another from the cardiac ganglion of the lobster.

2. It is argued that, unless the current density can be determined across the strategic portion of the cell membrane, this is the most suitable measure of the intensity of imposed currents which can exert an effect on the probability of firing of a neuron. The transmembrane potential does not provide such a measure.

3. In the most effective axis of polarization, it was found that a voltage gradient in the neighborhood of 0.1 mv/100 μ markedly influenced active cells. Currents of more than 20 times this value are required to fire a silent cell, even if it has been poised, i.e., the adapting stretch receptor, under a physiological degree of stretch.

4. The actual value of the critical voltage drop across the essential structure can only be smaller than this, and it may be much smaller. The transmembrane potential change with polarization may be from 0 to nearly one-half this value and is thus, at the most, several orders of magnitude smaller than the changes in membrane potential for threshold electrical stimulation or for several cases cited from the literature associated with alteration in activity or with inhibition or excitation.

5. The findings may mean that exceedingly critical firing levels in voltage across the membrane exist which would have to be confined to a certain portion of the cell near one of the poles relative to the effective axis of polarization. Alternatively, it is supposed that the imposed current acts by creating or increasing a gradient between different portions of the cell membrane, not across it but between one point on the surface and another. These possibilities are not mutually exclusive, and they suggest two new or little-considered parameters of neuronal state critically significant in determining activity over and above other conditions.

6. The great sensitivity of neurons to small voltage differences supports the view that electric field actions can play a role in the determination of probability of firing of units in ganglionic masses, in response to physiologically available currents. If true, this conclusion emphasizes the significance of morphology of the cell and of architectural arrangement of groups of neurons and their dendritic ramifications.

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