Modulation of Activity of One Neuron by Subthreshold Slow Potentials in Another in Lobster Cardiac Ganglion

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ABSTRACT A direct demonstration is given of interaction between specific neurons without impulses, *via* graded slow potentials electrotonically spread from one cell to another. Repetitive polarizing or depolarizing current pulses of 50 to 200 msec. and subthreshold intensity were passed through an intracellular electrode in the soma of a follower cell of the isolated ganglion. When the frequency is near the natural rhythm of impulse bursts corresponding to heart beats and arising in a pacemaker cell 5 to 10 mm. posteriorly, the bursts rapidly become synchronized with the pulses. The effect disappears upon withdrawing the intracellular electrode. Brief pulses or full spikes in the follower are not effective. Hyperpolarizing long pulses attract the burst to a fixed period after the end of the pulse, depolarizations after the beginning of the pulse. The natural rhythm promptly reappears when the pulses are stopped and occasionally breaks through during weak repetitive pulses. Current pulses in postsynaptic cells also alter the threshold of a presynaptic neuron to externally applied stimuli. Some kind of direct, low resistance pathway for electrotonic spread, discriminating against spikes because of their brevity, is inferred, providing a basis for subthreshold interaction which is specific and not by way of a field effect. Due to the sensitivity of modulation of ongoing rhythms, electrotonic currents can be effective even after decrementing over several millimeters.

INTRODUCTION

The possibility that neurons may interact with each other without the occurrence of nerve impulses, but only *via* graded, subthreshold activity has attracted interest but has not been directly tested. Strong suggestions that such interaction occurs have been adduced (see Gerard (1941, 1953), Bullock (1958)). The present report describes a direct demonstration in a ganglion which is maintaining its natural rhythm of impulse bursts corresponding to heart beats.

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Watanabe (1958) and Hagiwara, Watanabe and Saito (1959) discovered the existence of relatively low resistance electrical pathways between large anterior cells in the cardiac ganglion of spiny lobsters. D.C. potentials or long pulses applied internally in one cell could be seen, attenuated and rounded, in another cell—but only if both electrodes were intracellular. Some connection had to be postulated, possibly a fine protoplasmic bridge with at most a membrane separating the cells having a resistance much lower than ordinary cell membrane. These cells are normally followers in the formulation of a heart beat burst and are driven by a common pacemaker burst such that they show coincident synaptic potentials. There is little basis therefore for giving functional importance to the exchange of slow potentials between them.

In the present experiment we essayed to look for similar spread of slow potentials between follower and pacemaker. Here an influential role would be possible since it is precisely in the case of an ongoing rhythm that neurons exhibit an exquisite sensitivity to weak currents—heretofore known from externally imposed polarizations (Terzuolo and Bullock (1956)). Moreover this role would be interesting because it would provide a feedback from follower to pacemaker where until now no feedback had been found, looking at the effects of induced impulses. The feedback would be positive in sign.

Materials and Methods

Repetitive polarizing or depolarizing current pulses of 50 to 200 msec. duration and subthreshold intensity (10^{-9} to 10^{-8}A) were passed through an intracellular electrode in the soma of a large cell of the isolated cardiac ganglion of *Panulirus interruptus*.

The technics of preparation and of electrode management and recording were essentially the same as already reported (*cf.* Hagiwara and Bullock (1957), Bullock and Terzuolo (1957), Watanabe (1958)). The lobster heart was isolated from the body through a dorsal opening in the carapace. The heart was opened by an incision in its ventral side. The ganglionic trunk, which is a longitudinal cord containing five large and four small cells (Alexandrowicz (1932)), was located under the microscope and was dissected out from the myocardium by needles in holders. Almost all myocardial tissue was removed from the middle part of the trunk. Branches from the ganglionic trunk and the extrinsic fibers were also cut near the trunk. The trunk was then mounted on a trough created by a piece of glass and wax in a Petri dish (Fig. 1). The four anteriormost large cells were placed on the piece of glass. Light was supplied from beneath through a system for darkfield illumination. The caudal part of the trunk was placed in a separate pool across an air gap. External stimulation or external recording was performed with a pair of platinum electrodes attached to the trunk at the air gap.

Glass capillary microelectrodes with tip diameters of less than 0.5 μ and filled with 3 M KCl were used. Usually two microelectrodes were inserted into one of the large cells, one for passing current and the other for recording the membrane potential.

For the physiological saline natural sea water was found best in keeping the regularity of the spontaneous burst. In favorable preparations the heart beat burst discharges continued for more than 5 hours. Experiments were performed at room temperature which ranged from 21–27°C.

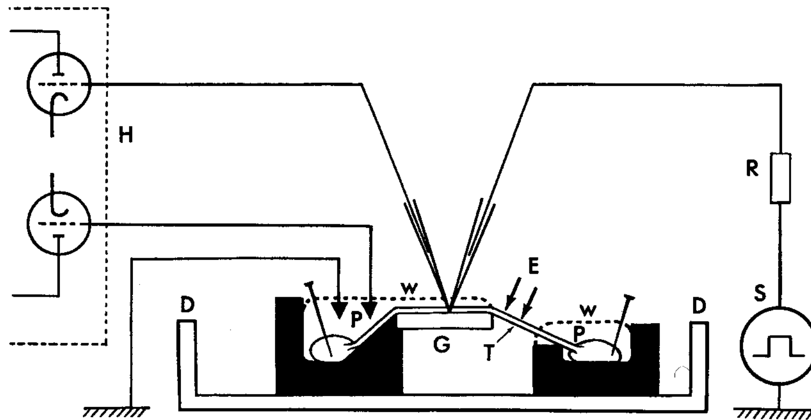


FIGURE 1. General arrangement of experiment. Two pools (*P*, *P*) are situated in a Petri dish (*D*). *T*, ganglionic trunk. *G*, a piece of glass which supports the ganglionic trunk. *W*, water surface. *E*, external electrodes for stimulation or recording. *S*, square pulse generator for supplying the polarizing current. *R*, series resistance. *H*, differential preamplifier.

RESULTS

A. The Effect of the Polarization of a Follower Cell on the Rhythm of a Pacemaker Cell

The effective resistance of the cell membrane of follower cells of the lobster cardiac ganglion commonly falls between 1 and 5 megohms, so that to produce electrotonic potentials of about 10 mv., currents are applied through the internal electrode between 10^{-9} and 10^{-8} A.

When polarizing current pulses of this intensity are applied repetitively to one of the large cells, they always cause some effect on the rhythm of the spontaneous discharge, and under some conditions the natural frequency of the spontaneous burst changes and approaches the applied pulse frequency. In Fig. 2, an example is presented. In the left column the natural burst with a frequency of about 0.3 per second is shown. In the central column repetitive hyperpolarization was applied to one of the large cells and the natural burst, which is driven by a pacemaker cell near the posterior end of the ganglion and is recorded here as a slow burst in the follower cell, goes into synchrony with these pulses. In the right column the current was outward so that repetitive subthreshold depolarization was imposed on the follower cell membrane.

This time, too, the burst discharges come into synchronization with the applied pulses.

As seen in Fig. 2, the phase relation between the pulse and the burst is different according to the polarity of the applied current. In the case of anodal polarization, the burst does not superimpose on the applied pulses, and most frequently it follows them with a more or less fixed latency which ranges from 0.1 to 0.2 sec. On the other hand in the case of cathodal polarization the burst appears following the beginning of the applied pulse so that there is a strong tendency for the burst to superimpose on the applied depolarization. The burst avoids hyperpolarization and is attracted to depolarization.

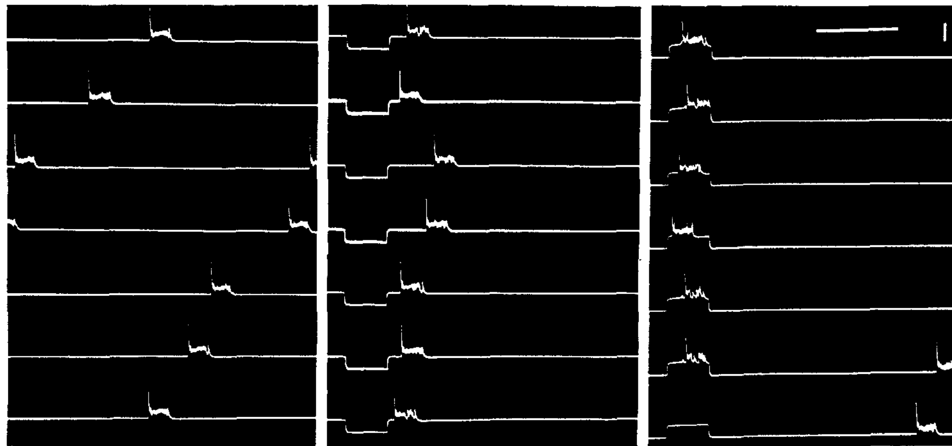


FIGURE 2. The effect of repetitive polarization on the rhythm of burst discharge. The picture was arranged from a continuous moving film which was cut every 3.7 sec. Time goes from top to bottom.

Left, spontaneous burst discharge.

Center, repetitive hyperpolarization with synchronized burst discharge.

Right, repetitive depolarization with synchronized burst discharge.

An escape is seen at the bottom of the record.

Calibrations, 10 mv., 1 sec.

The major effect of the repetitive hyperpolarization is the prolongation of the interval. (See the section below.) The driving effect of repetitive hyperpolarization appears most clearly when the applied pulse frequency is lower than the natural frequency. When the applied pulse frequency is higher than the natural frequency, the synchrony of the pace is established only temporarily if at all. When the pulse frequency is higher than the natural frequency, repetitive depolarization is more effective than hyperpolarization in driving the heart beat.

There are several ways to represent the effect of synchronization. Two simple ways are adopted in Fig. 3. In each diagram the lower line shows the

interval between successive bursts, whereas the upper line shows the interval between the end of the current pulse and the beginning of the burst discharge ("latency"). The latencies shown before the application of effective strengths of pulses in A and C are measured from ineffective pulses of slightly different frequency from that of the bursts, and are constantly changing, showing that the fixed latency which appeared during effective pulse application is not due to coincidence. In A, the synchronization was very rapid and complete. The natural burst interval of 664 ± 62 msec. changes to 800 ± 35 msec. after two applied pulses; the latency becomes fixed at a value of about 130 msec.

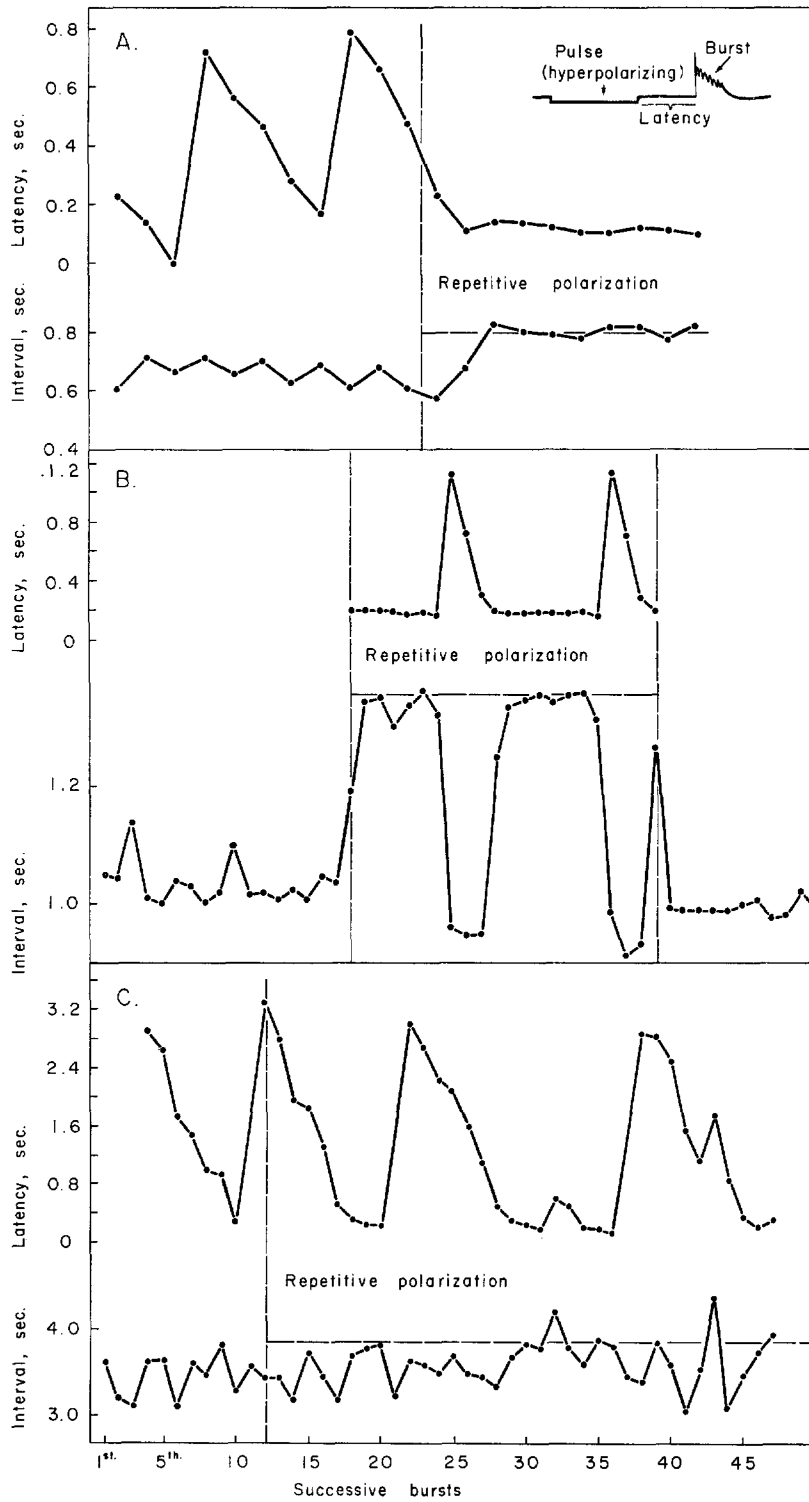
Fig. 3B shows a longer record. The burst interval before pulse application ranges from 1.00 sec. to 1.14 sec. with a mean value of about 1.04 sec. After one or two applied pulses the interval changes and attains a value very near to the applied pulse interval (1.35 sec.). After several synchronized bursts however, the burst interval changes back again to a value even lower than the original and then returns to the applied pulse interval. Apparently two rhythms are competing during the pulse application. This phenomenon, which may be called escape from the driving effect, makes its appearance again in this record. During the period of escape, the fixed value of latency also disappears, of course.

In Fig. 3C, an example is represented in which the effect of synchronization is weaker than in the previous examples. Because of the relatively large fluctuation of the basic burst interval, and because escape occurred often, it is difficult to recognize a definite change of the frequency in the interval diagram (lower trace). In the latency diagram (upper trace), however, the effect of polarization is clearly seen and for a limited period it is justifiable to speak of synchronization: in the middle of the record, where the latency is minimal for nine heart beats.

THE EFFECT OF A SINGLE PULSE The conditions for the establishment of synchronization are complex. It depends on the frequency, duration, and intensity of the applied pulse, and the frequency of the original burst.

It seems simpler to examine the effect of single pulses on the burst discharge. Fig. 4 shows one such experiment. An inward current pulse was applied to the membrane of one of the large cells, causing a hyperpolarization of about 8 mv. The interval between the bursts was rather constant in this material, so that it was possible to show that the imposed pulse causes an increase of the interval. The mean interval between bursts is 0.88 sec. with a standard deviation of 0.07 sec. whereas the intervals imposed by the hyperpolarizing pulses are 1.10, 1.03, 1.19 sec., respectively. The interval may increase more than 100 msec. due to the applied pulse.

The next interval, during which the current pulse ceases is significantly shorter than the average interval. In records in Fig. 4, the values are 0.54, 0.53, 0.52 sec., respectively.



A.
Pulse
(hyperpolarizing)
Burst
Latency
Latency, sec.
Interval, sec.
Repetitive polarization
0.8
0.6
0.4
0.2
0
0.8
0.6
0.4
B.
1.2
0.8
0.4
0
Latency, sec.
Repetitive polarization
1.2
1.0
Interval, sec.
C.
3.2
2.4
1.6
0.8
0
Latency, sec.
Repetitive polarization
4.0
3.0
Interval, sec.
1st.
5th.
10
15
20
25
30
35
40
45
Successive bursts

In most cases an inwardly directed current pulse causes elongation of the interval during which the current starts. There are, however, many exceptions in long records and especially when the basic rhythm of the burst is not sufficiently regular. Even in such cases, statistical treatment shows that there are significant effects of the hyperpolarizing pulse.

In Fig. 5 histograms are made from the intervals in a long record. The upper is from parts of the film which are free from the imposed current. The mean interval is 0.78 sec. with a standard deviation of 0.06 sec. The histogram ranges from 0.6 to 1.0 sec., and furthermore, the shape is not a unimodal distribution; it has at least two peaks. One of the peaks has a value of 0.8 sec. whereas another has a value of 0.72 sec. This phenomenon is not uncommon (*cf.* for example, Fig. 3A). The lower histogram was made from the burst intervals during which the hyperpolarizing current begins. It is clear that the general distribution shifts to the right. The mean value of the intervals is 0.89 sec. with a standard deviation of 0.06 sec. The shift of the average was about 100 msec. The shapes of the distributions are quite similar in the two graphs. Although the number of intervals for the lower histogram (17) is not sufficient for a definite conclusion, it seems probable that the lower distribution is formed by a horizontal movement of the upper distribution. In other words, if one supposes that the effect of the anodal polarization is nothing but to add about 100 msec. to the natural interval, the similarity between the shapes of the upper and lower histograms would be easily explicable.

Similar treatment of the intervals during which hyperpolarizing current pulses end shows that they are significantly shorter than the controls (mean, 0.69 sec. with a standard deviation 0.09 sec.). The main reason for this effect is that the latency, from the end of the current to the beginning of the first following burst, is fairly constant (100 to 300 msec.) even when the interval between the preceding burst and the end of the current pulse changes widely. Exceptional latencies appear only when the preceding burst is too near (less than 200 msec.) or too far (more than 700 msec.) from the end of the current: latencies then become larger and smaller respectively

Although intensity or voltage clearly had to be above some value to be effective, efforts to study the function of intensity were frustrated by the lack of gradation in synchronization. Virtually speaking, it was either present or absent.

FIGURE 3. The effect of repetitive hyperpolarization on the rhythm of the pacemaker represented by latency diagrams and interval diagrams. The serial number of the successive bursts is on the abscissae. In each frame the upper trace indicates the change of latency whereas the lower trace indicates the change of interval. Vertical broken lines appearing in each frame indicate "on" or "off" of the repetitive polarization and the duration of the applied repetitive polarization is shown by horizontal broken lines.

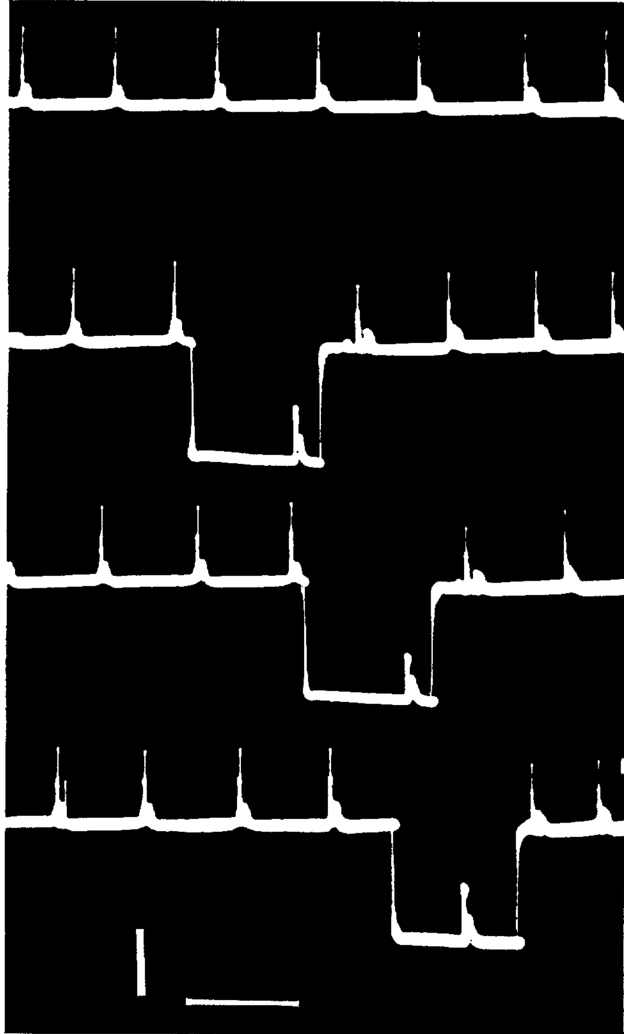


FIGURE 4. The effect of single hyperpolarizing pulses on the natural burst interval.
Top record, natural burst discharge.
Lower records, polarizations are applied at long intervals (more than 10 sec.) and randomly.
Calibrations, 5 mv., 1 sec.

The Effect of Brief Pulses or Spikes in a Follower Cell on the Pacemaker Activity

It has been shown by Otani and Bullock (1959) that the spikes elicited in a follower cell do not cause any effect on the pacemaker activity. On the other hand the results above show that a potential change in a follower cell does

cause some effect on the pacemaker, so that there is an apparent discrepancy between these results.

To examine this point, the effect of shorter pulses or spikes on the pacemaker was examined, under conditions in which the longer pulses cause a clear synchronization. One example is shown in Fig. 6. The spontaneous burst discharges of 0.52 per sec. (in the left column) came into synchronization with applied pulses of 0.62 per sec. (in the central column). External

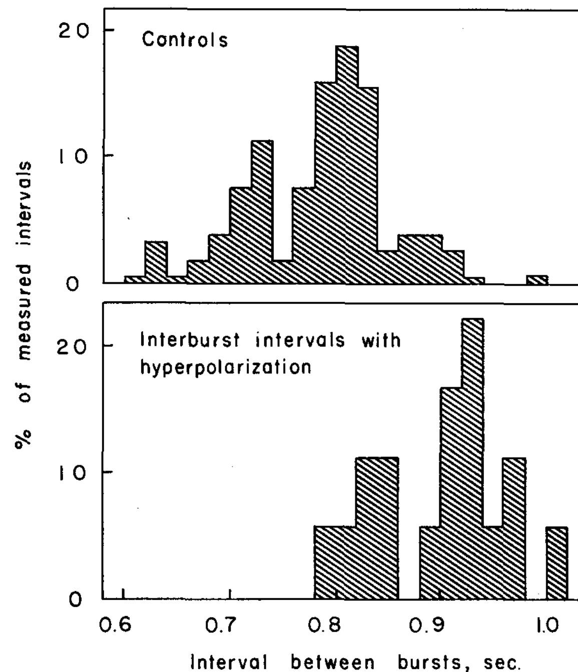


FIGURE 5. Burst discharge interval histogram and its change by polarizing pulse application.

Upper, natural burst intervals.

Lower, intervals during which a hyperpolarizing current pulse begins.

recording confirmed that the applied pulses were, though outward to the membrane, well under the threshold so that no follower cells fired directly by outward current itself. The burst discharges always originated from the normal pacemaker regions in small cells. Thus, the synchronization cannot be attributed to spike feedback to the pacemaker, but should be attributed to an effect which is directly caused by slow depolarization in a follower cell.

When the duration of the applied pulses was reduced to less than 50 msec., the effect on the synchronization became remarkably smaller. By increasing the intensity of the current it was possible to elicit spikes in the penetrated

cell. Even under such conditions any effect there might be was still too small for complete synchronization (right column).

The experiment described above is, on the one hand, a confirmation of the results obtained by Otani and Bullock (1959). On the other hand, it shows conclusively that a certain duration is essential to cause the synchronization effect. Short pulses were, including conducted spikes, not effective in causing synchronization. It seems highly probable that the system mediating this effect is a kind of low pass filter, like the routes assumed for the electrical connection found between large cells in the same ganglion (Watanabe (1958), Hagiwara *et al.* (1959)). It seems that only the slow components of the potential change in follower cells reach the pacemaker region, and cause

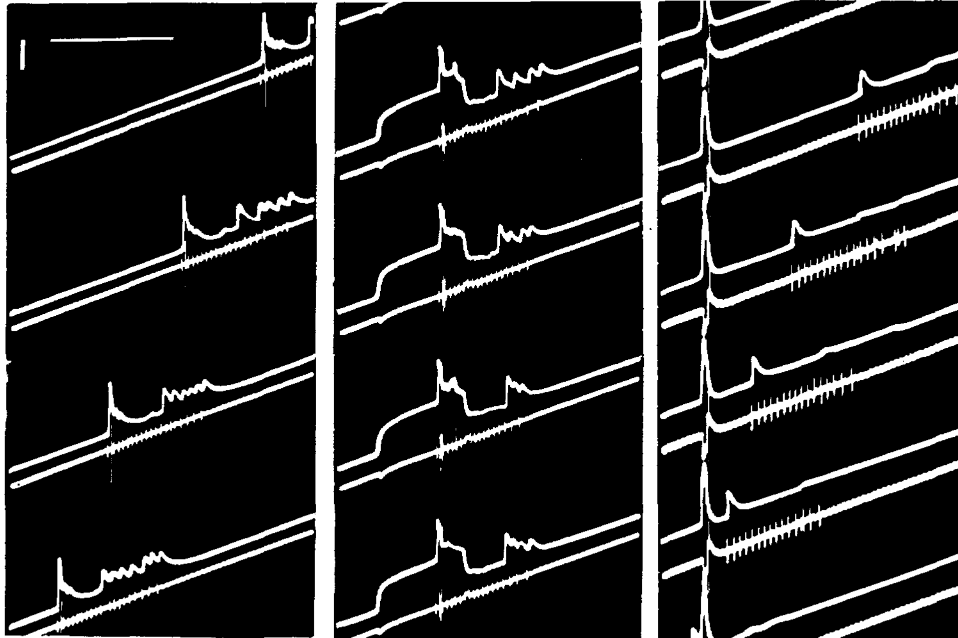


FIGURE 6. The effect of longer and shorter depolarizing pulses on the rhythm of the burst discharges. Time goes from bottom to top.

Upper beam, intracellular recordings.

Lower beam, external recordings without calibration.

Left, natural burst.

Center, synchronization of the burst with an applied pulse of about 0.3 sec. duration.

Right, Disappearance of the synchronization by reducing the duration of applied pulse. Intensity of the pulse is much increased so that a spike is elicited by the pulse. Synaptic potential had decreased in size. Sensitivity of the external recording has been doubled.

Calibrations, 10 mv. (intracellular-upper beam), 0.5 sec.

some effect, probably by changing the time course of the slowly rising depolarization called the pacemaker.

B. The Effect of Polarization of a Follower Cell on the Excitability of the Presynaptic Neuron

It has been shown above that the membrane potential in a follower cell influences the frequency of a pacemaker cell. Since under normal conditions the pacemaker is located in one of the small posterior cells which are presynaptic to the large anterior cells, the effect described above is a kind of antidromic effect, in the sense that the postsynaptic events have some effects on the presynaptic element. From this consideration the question arose whether the potential change in a postsynaptic cell membrane can cause any other effect than on the generation of the periodic burst discharge. The experiments described below were based on the discovery that there is a threshold change in the presynaptic axon when the membrane potential of the postsynaptic cell is artificially changed.

After inserting two microelectrodes in one of the large cells, stimulation was applied externally to a part of the ganglionic trunk by the use of a pair of platinum wire electrodes. These electrodes were applied to the caudal portion of the trunk 5 to 8 mm. behind the penetrated cell. This is presumably between the fifth (posteriormost) large cell and the small cell group, though the exact relation to the cell bodies was not accurately determined by direct observation. The stimulating pulse to the wire electrodes was less than 1 msec. in duration; its circuit was isolated from ground. With sufficient intensity a synaptic potential was observed in the large cell after a latency of less than 10 msec. and the usual small spikes were sometimes superimposed on this (Hagiwara and Bullock (1957)).

In Fig. 7, the effect of hyperpolarization imposed on one of the large cells on the threshold of the presynaptic fiber is shown. The intensity of the external stimulus applied to the trunk was just above the threshold and was kept constant throughout the three pictures which were taken successively. The left picture shows a control, in which a synaptic potential of about 15 mv. amplitude appears after the stimulation. The polarizing current has not yet been applied. The second smaller synaptic potential is presumably a reflex from other cells.

In the middle picture, a hyperpolarizing current pulse of 8×10^{-9} A was applied to the cell membrane through the current electrode; this caused a hyperpolarization of about 23 mv. The synaptic potential in response to the stimulus has disappeared in an all-or-none manner, suggesting a failure of the presynaptic spike process to reach a threshold for transmission. In other trials on the same preparation it was shown that raising the strength of the

stimulus to the trunk restored the synaptic potential. In the picture on the right, the current electrode was withdrawn from the penetrated cell. The hyperpolarization disappeared immediately, and the synaptic potential reappeared in an all-or-none manner, though the intensity of the current did not change at all. This picture shows that the disappearance of the synaptic potential with intracellular current application is not due to the external field in the tissue or Ringer solution.

The experiment shows that the change of membrane potential in a follower cell causes a change in threshold of the presynaptic fiber. When a hyperpolarizing pulse is applied to the follower cell, the threshold of the presynaptic

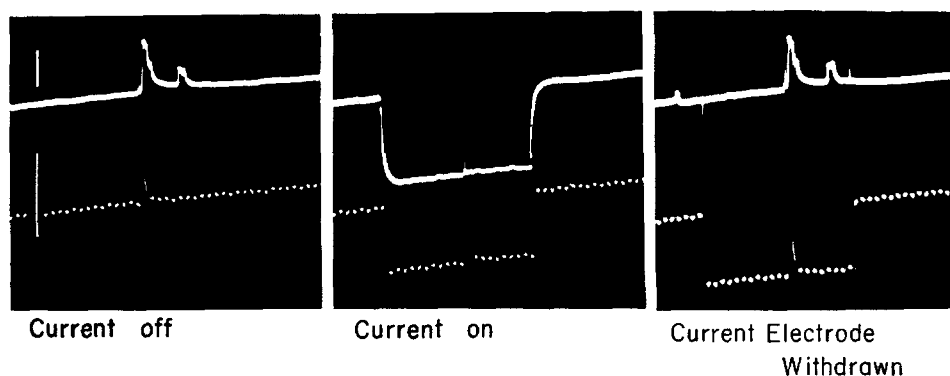


FIGURE 7. Synaptic potentials elicited by a threshold trunk stimulation and their abolition by hyperpolarization of the postsynaptic cell.
Upper beam, intracellular potential recording. Calibration, 10 mv.
Lower beam, current recording. Calibration, 10^{-8}A.
Time is indicated by lower beam which is interrupted every 10 msec.

fiber increases; depolarization in a follower cell membrane causes a decrease in threshold of the presynaptic fiber.

The value of the change of the threshold is different from preparation to preparation, even when the applied polarization is much the same. A 20 mv. hyperpolarization in one preparation caused an increase of 35 per cent over the control value, whereas in another preparation there was less than a 10 per cent increase. In almost all cases the threshold shows considerable spontaneous fluctuation, frequently as much as 10 per cent. In such cases determination of the change of the threshold becomes inaccurate. It is conceivable that at least a part of this fluctuation is due to subthreshold activity of the pacemaker cell. Fortunately, the actual fluctuation of the threshold has a rather slow time course, so that it is possible to regard the threshold as constant for a few seconds. It was possible to express the change of the threshold by comparing the stimulating intensity just before and after the application of the polarizing current.

Using this procedure, it was possible to measure the time course of the threshold change from the beginning of the current pulse (Fig. 8). The most remarkable property was that the rise of the threshold was very slow compared to the time course of the electrotonic potential. The latter saturates within 30 msec. whereas the threshold change does not reach its maximum in less than 100 msec. This conclusion was confirmed by another experiment. The interval between the beginning of the current and the external stimulus was changed from 60 to 120 msec. and for each interval a change in threshold was determined. With critical stimulating intensity it was always possible to demonstrate that the threshold is higher at later stages of the hyperpolarization and this in spite of the opposite effect which would result from any accommodation which might be occurring. Because this kind of experiment could be

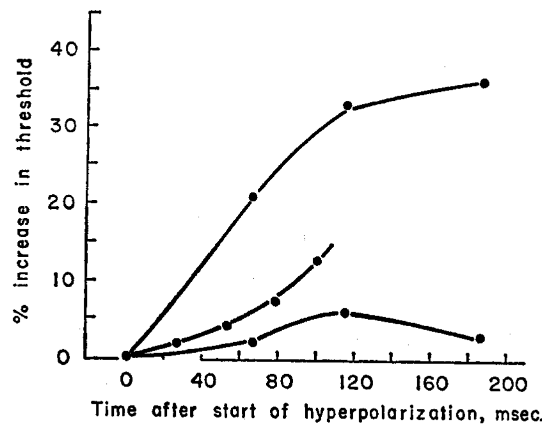


FIGURE 8. Time course of the threshold change of three presynaptic axons, caused by hyperpolarization applied to the postsynaptic cell.

repeated many times within a short period and always with consistent results, it is safe to conclude that the rising phase of the threshold continues for more than 100 msec.

This slow rise of the threshold suggests that the slow component of the normal synaptically evoked potential change in follower cells (Bullock and Terzuolo (1957)) is essential for changing the threshold of the presynaptic fiber. It seems quite appropriate to interpret these results by the assumption that this threshold change is due to an electrotonic spread from the follower cell to the presynaptic fiber through a kind of connection, which is just the same interpretation as for the mediation of the effect of synchronization.

DISCUSSION

The principal interest in these findings is the evidence they afford of interaction between neurons without impulses, on a specific cell to cell basis

rather than by way of field effects. Subthreshold cross-talk has been postulated (Gerard (1941, 1953), Bullock (1958)) but this is the first direct demonstration to our knowledge. It is conceivable that this is quite common because it would be easy to overlook and there is considerable presumptive reason to believe that communication without impulses is important in neuropiles and gray masses.

The mechanism of the interaction is shown to be *via* a direct electrical connection between the inside of one neuron, into which a long subthreshold pulse is injected and the pacemaker region of another. Withdrawal of the stimulating electrode to just outside the follower neuron stops the effect. Some relatively low resistance path must exist between neurons. If a membrane of the same resistance as ordinary cell membrane intervenes, the extracellular electrode should be as effective as the intracellular. It is not shown that a protoplasmic anastomosis exists but if not, a membrane of markedly low resistance separates the neurons.

There is no sufficient reason to doubt that the two neurons are distinct. Even if there should prove to be an anastomosis, it would be a fine, non-impulse–propagating bridge between normal cellular units with quite a different time course of activity. This would be one more special exception like the multiple cells of origin of the squid third order giant fiber, not a denial or material weakening of the doctrine of independence of neurons.

The distance over which a purely electrotonic influence can be felt is here of the order of 5 mm. We may reasonably guess that the decrement with distance for such a passively spreading membrane potential change is of the order of one-half for each millimeter. Even if the potential change attenuates to considerably less than 3 per cent of that applied in the follower cell, where our pulses had to be several millivolts, it seems likely that the high sensitivity known (Terzuolo and Bullock (1956)) for D.C. modulation of ongoing rhythms is not being strained. This exquisite sensitivity—in terms of voltage gradient in the external medium, 0.1 mv. per 0.1 mm. is effective in the crayfish stretch receptor cell, and 0.03 μv. per mm. in the electroreceptors of gymnarchid fish (Lissmann and Machin (1958)), is probably employed normally in some way. Besides the possibility of field influences as in electric fish orientation and perhaps some modulation of neural activity by brain waves, the present mechanism of specific electrotonic connections seems not unexpected in this light.

The regularity of a rhythm like the heart beat means not only that the critical threshold potential for triggering the event is remarkably stable but also the rate of rise of the pacemaker potential between beats. This then could be the process which is easily altered by a small superimposed voltage, bringing it to the threshold level a little sooner or later, according to the sign of the added voltage.

The feedback which is provided in the present case is positive in sign. Heretofore no feedback could be demonstrated by eliciting impulses in follower cells *via* internal electrodes (Otani and Bullock (1959)). Since at least some follower cells characteristically show a large slow depolarization during a burst, there may be considerable signal feedback electrotonically to accelerate the pacemaker and hence possibly leading to an earlier cutoff of its own burst and this in turn shortening the next interburst interval.

Note Added in Proof The question whether electrotonic connections between cells are a peculiarity unique to lobster heart ganglia can already be answered in the negative. Dr. M. V. L. Bennett, Dr. S. M. Crain, and Dr. H. Grundfest permit me to refer to experiments on the supramedullary neurons in puffer fish supplementary to the papers of these authors (*J. Gen. Physiol.*, 1959, **43,** 159–250). When a polarizing electrode is in one cell and a recording electrode is in another, slow potentials are seen to spread with less attentuation than if either electrode is just outside. Such connections probably explain the curious synchronization of firing described in the cited papers. (See Bennett, M. V. L., *Fed. Proc.*, 1960, **19,** 282.)

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