FURTHER DEVELOPMENTS OF A. A. UKHTOMSKY'S THEORY OF THE PARABIOTIC ORIGIN OF THE REFRACTORY PHASE*

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The present work constitutes the first experimental proof of the theory of A.A. Ukhtomsky [9] that the refractory phase of the nerve is a short lasting condition of parabiosis.

Many results have been published which suggest that the refractory phase is a manifestation of parabiosis. D.G. Kvasov and G.E. Zeberg [7] showed that the minimal time taken for cathode block, established by N.E. Vvedensky's method of minimal polarization, to disappear, corresponds to the duration of the absolute refractory phase.

D.S. Vorontsov [4] observed that during the relative refractory phase, the cathode of a strong inductive stimulus inhibits the nerve impulse, particularly when the nerve is treated with potassium. As a result of this, the cathode of a second stimulus increases the duration of the absolute refractory phase, while the anode reduces it. Similar effects of the action of the anode and cathode of a second stimulus on the nerve impulse at the very beginning of the relative refractory phase have been described by the Japanese authors Otani, Ono and Usio [12]. Consequently, in the relative refractory phase, the anode and cathode affect the development of a nerve impulse in a way which resembles their action on a nerve which is in a condition of parabiosis due to potassium, i.e. the cathode increases and the anode decreases it (M.I. Vinogradov) [3].

Thus it may be supposed that during the relative refractory phase the nerve passes into a short period of parabiosis. If this is so, at the very onset it ought to be possible to observe the typical stages of parabiosis, namely the paradoxical and equalizing phases. Indirect experimental evidence for this idea is given by A.N. Kabanov [6]. However there is no direct proof that a parabiotic stage occurs at the beginning of the relative refractory phase. Professor N.V. Golikov has told us that in 1930, A.A. Ukhtomsky entrusted him and his student P. Shmidt to investigate this problem. However technical reasons prevented him from doing so.

EXPERIMENTAL METHOD

Monophasic action potentials from the isolated sciatic nerve of the frog were recorded on a four channel cathode ray oscillograph [5].

Three of the beams of the cathode ray oscillograph were used. Two-millisecond time markings from a 500 c/s tuning fork generator were recorded on the upper trace, stimuli from a special generator on the middle

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trace, and the nerve action potential on the bottom trace. The generator allowed 2 stimuli of triangular or square wave form of pre-established length to be delivered. A stimulus length of about 0.5 milliseconds was used. The interval between these two stimuli could be varied from 0 to 100 milliseconds. The amplitude of the stimuli could also be changed over a considerable range. The setup was arranged to give a steady picture, so that both photography and visual observation were possible. The steady picture on the screen was obtained by not using isolated pairs of stimuli, but a series of them at a frequency of 100 per second. Besides being able to stimulate the nerve with the series of double stimuli, a single pair of stimuli could be applied once, as in the usual pendulum arrangement. Both methods gave the same result. The traces shown below were recorded using the steady repetitive picture.

EXPERIMENTAL RESULTS

Figure 1 shows five oscillograms recorded in succession from the same nerve. Oscillogram a shows the action potential developed in response to the first stimulus. Oscillogram b shows two action potentials: the first large potential is due to the first stimulus, and the second small one to the second stimulus, delivered 2 milliseconds after the first one, i.e. at the very beginning of the relative refractory phase. Oscillogram c is taken with the same interval between the first and the second stimuli but with a much greater amplitude of the second stimulus, with the result that the second action potential has almost disappeared. If the amplitude of the second stimulus is now made smaller, as is shown in oscillogram d , then the second action potential again appears. Oscillogram e shows that if a single stimulus is given again,the picture obtained is precisely the same as oscillogram a , which shows that the condition of the nerve has not changed. Comparison of b, c and d shows that the paradoxical phase of parabiosis is occurring.

When the interval between the first and second stimuli is increased the equalizing stage of parabiosis occurs. Figure 2 shows five oscillograms taken from the same nerve used in Fig. 1. In order to be able to show the greatly increased amplitude of the second stimulus, a reduced amplification was used for the stimulus trace. The first stimulus here, as in Fig. 1, is supramaximal. This time the second stimulus was applied approximately 4 milliseconds after the first, i.e. somewhat longer after the beginning of the relative refractory phase than in the previous experiment.

While maintaining the interval between the stimuli constant, the amplitude of the second stimulus was increased (Fig. 2, oscillograms b,c ,d and e). The action potential developed in response to the second stimulus, increases at first (Fig. 2,b), and then remains at a steady value (Fig. 2, c,d and e).

The results of the experiment shown in Fig. 2, b,c,d, and e are to be interpreted as showing the equalizing stage of parabiosis.

DISCUSSION

What objections are there against paradoxical changes in the action potential occurring in response to variation in stimulus strength, as shown in the oscillograms? On increasing the amplitude of the second stimulus, the action potential evoked by it at the very beginning of the relative refractory phase almost completely disappears. It follows that the activity of all the fibers of the mixed nerve trunk has been suppressed.

Are not other characteristics of the action potential also changed with increase of stimulus strength? P.O. Makarov [8] has shown that the length of the refractory phase may be changed, for instance by alteration of the shape or duration of the stimulus. However our results contradict this idea. They show that the shape, rate of rise and duration of the stimuli remained unchanged for the whole of the experiment; only the strength of the second stimulus is changed. This allows us to attribute changes in the size of the action potential solely to change of stimulus strength.

It seems paradoxical to say that variations in the amplitude of an action potential which obeys the "all or none" law, represent the equalizing stage of a functional parabiosis which is itself derived from an action potential, or, more precisely, from the catelectrotonic portion of a spike.

Approaching the problem in a different way, it may be asked whether the equalizing stage of parabiosis does not itself constitute the means whereby the control is effected over the nerve impulse. This was the standpoint of L. M. Shereshevsky and N.A. Shoshina [11] and A.A. Ukhtomsky [9]. They considered that the alteration of the action potentials must be interpreted as representing the equalizing phase of parabiosis. The problem of the reason for the autoregulation of the nerve impulse was considered by N.E. Vvedensky [2]. Our experimental results showing the equalizing stage of parabiosis in the relative refractory phase go some way towards supplying the answer to the problem raised by N.E. Vvedensky, and support the view of L.M. Shereshevsky, N.A. Shoshina and A.A. Ukhtomsky.

It is not possible here to go into a detailed discussion about the mechanism of autoregulation of nerve impulses. We will merely refer to the work of M.S. Averbakh and D.N. Nasonov [1] which deals with this problem. They consider autoregulation of nerve impulses to be based on only one of the indices of the functional condition of the nerve, namely its excitability.

In view of the results we have described here, it must be supposed that in the mechanism of autoregulation, not only does the excitability of the nerve play an important part but so also does the parameter of physiological lability.

Thus we have shown experimentally, that during the relative refractory phase, the amplitude of the action potential of the nerve changes, according to the interval between the conditioning and the test stimulus, in accordance with the laws of the parabiotic process, so that the paradoxical and the equalizing stages of parabiosis are shown. The existence of these stages has also been demonstrated in the case of the motor nerve endings.

It appears likely that the equalizing stage of parabiosis plays an important part in the mechanism of the control of the nerve action potentials.

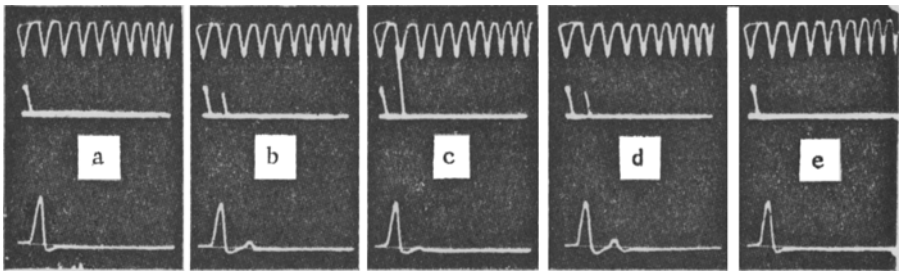

Fig. 1. Demonstration of the paradoxical stage of parabiosis at the very beginning of excitation of a nerve after the first maximal stimulus (at the beginning of the relative refractory phase).
Curves from above downwards: upper traces – time markings 500 c/s, middle trace – stimulus; lower trace -- nerve action potential.
Oscillogram section a,b,c,d and e explained in text.

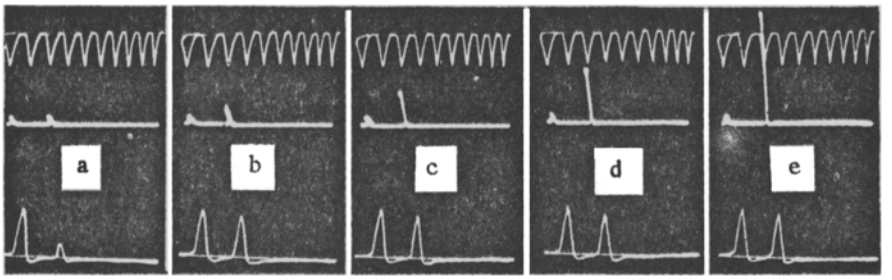

Fig. 2. Demonstration of the equalizing stage of parabiosis during recovery of excitability of a nerve after an initial maximal stimulus (in the relative refractory phase).
Key: same as for Fig. 1.

SUMMARY

In 1927 A. A. Ukhtomsky suggested that refractory phase of the nerve is the condition of short parabiosis. It is probable that during the relative refractory phase the nerve gradually comes out of parabiosis. If this is the case – then at the very beginning of it the typical stages of parabiosis should be found, i.e. the paradoxical and the equalizing. The author's experiment demonstrated that this actually takes place. It was experimentally established that during the relative refractory phase the amplitude of the potential of the nerve action changes. This change depends on the interval between the experimental and testing stimuli with the regularity of the parabiotic process. Paradoxical and equalizing stages of parabiosis were revealed at the beginning of the relative refractory phase.

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