THE INFLUENCE OF CERTAIN CHOLINERGIC SUBSTANCES ON ACCOMMODATION IN A NERVE TRUNK

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Previously [1] it has been shown that prevention of acetylcholine formation by pancreatectomy increases the rate of accommodation in the sciatic nerve of the frog, and that the injection of small amounts of acetylcholine reduces accommodation in this nerve.

In the present work we have made a comparative study of the influence of 2-methylnaphthaquinone, eserine, atropine, and acetylcholine on accommodation in this nerve. It is known that 2-methylnaphthaquinone interferes with the synthesis and with the liberation of acetylcholine [2, 5, 6].

EXPERIMENTAL METHOD

The experiments were carried out on a nerve-muscle preparation of the frog (R. ridibunda). Accommodation in the sciatic nerve was investigated by the usual method [1]. After determination of the initial amounts of accommodation either the whole preparation or the nerve alone was placed in a solution of the substance to be studied in Ringer, and successive measurements were made at 30 min intervals. A 2nd preparation of the same frog was placed in Ringer, and served as control. We performed 26 experiments with 1:10,000 2-methylnaphthaquinone, 15 experiments with 1:5,000 and 1:500 eserine, 15 with 1:1,000 atropine, and 10 with 1:10,000, 1:5,000, and 1:500 acetylcholine.

EXPERIMENTAL RESULTS

The rate of accommodation and the rheobase of the control preparations in Ringer showed practically no change over a period of 2-3 h. After a longer time the preparations in Ringer showed a continuous reduction in the rate of accommodation of the nerve, and after 16-18 h the accommodation constant had increased on average from 17.2±2.5 msec during the first few hours after the preparation had been made to 27.6±3.1 msec, i.e., by more than $1\frac{1}{2}$ times (Fig. 1a). The rheobase increased on average from 1.45 to 1.69 v, i.e., by 16.5%.

During the action of 2-methylnaphthaquinone (1:10,000) we observed a regular increase in the rate of accommodation; the slope of the curves (Fig. 1b) increased and the accommodation constant λ became shorter; in the first 30-40 min of the action the rate of accommodation showed no significant change, and it was not until later that it increased more or less regularly. Thus, the accommodation constant λ was reduced on average from 20.6±1.7 msec in the control preparations to 17±1.2 msec during 60 min of the action of 2-methylnaphthaquinone; after 90 min it had fallen to 12.3±1.6 msec, and after 120 min to 8±1.3 msec, i.e., during this time it had fallen to two fifths of its original value (Fig. 2). In contrast to the change of accommodation there was a much greater reduction in the excitability of the nerve, as determined by the rheobase; this change was noticed in the first 30 min of the action of the substance under investigation, and then the rheobase became more or less stabilized so that at the end of 2 h it amounted to 126% of its original value (an average of 2.26 v instead of 1.8 v in the control). Thus, the rate of change of threshold is not the same as the rate of change of accommodation, and the increase in the rate of accommodation is accompanied by comparatively small fluctuations in excitability.

A considerable increase in accommodation and shortening of the accommodation constant was observed also in

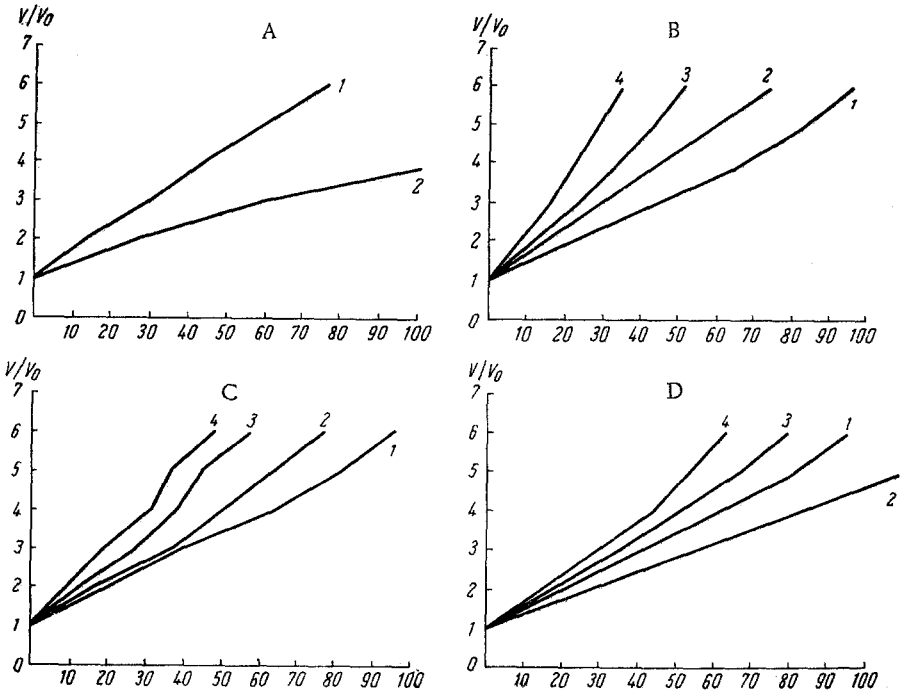

Fig. 1. Curves of accommodation in the sciatic nerve of the frog (mean values). a) (1) After 30 min, and (2) after 16-18 h in Ringer; b) (1) control, (2) after 60 min, (3) after 90 min, and (4) after 120 min of the action of 1:10,000 2-methylnaphthaquinone; c) (1) control, (2) after 30 min, (3) after 60 min, and (4) after 90 min of the action of 1:1000 atropine; d) (1) control, (2) after 35 min, (3) after 75 min, and (4) after 100 min of the action of 1:5,000 and 1:500 eserine. Abscissa) time of increase of stimulating current in msec; ordinate) threshold stimulus expressed as multiple of rheobase.

the case of atropine. Thus, even by the 30th min the accommodation constant had fallen on average to 16.1±1.8 msec, after 60 min it had fallen to 12.7±0.9 msec, and after 90 min it was 10.2±1.9 instead of 20.2±1.6 msec as in the control. Accordingly the curves of accommodation during the action of atropine rise more steeply (Fig. 1c). In contrast to the experiments with 2-methylnaphthaquinone these changes in accommodation which we have just described take place as a rule in association with an increased excitability of the nerve to direct current, but the graphs are not of the same shape (see Fig. 2). Because of the extent to which the accommodation changes, and because of the greater molar concentration used in this case we must suppose that atropine increases the rate of accommodation less than does 2-methylnaphthaquinone.

Eserine differs from the 2 previous agents in causing a marked biphasic change in the rate of accommodation. At a dilution of 1:5,000 during the first 30-45 min the accommodation constant λ increases on average to 25.3±2.4 msec as compared with 19.4±1.5 msec in the control. Subsequently the rate of accommodation begins to increase, and after 75 min the accommodation constant has fallen to 17.3±0.9 msec, and after 100 min to 15.4±4.4 msec. Accordingly the curves indicate a more rapid accommodation than in the controls and they have the concavity characteristic of high rates of accommodation (Fig. 1d). The same biphasic changes in accommodation were observed at all concentrations of eserine used.

The increased accommodation observed in the 2nd phase of the action of eserine is in line with results obtained when this substance was used previously [1], and when it was used to treat the stimulated part of the nerve [3]. We may note that the reduced rate of accommodation of the nerve during the 1st phase of the action of eserine is not very marked and does not reach even the level which was observed after prolonged action of Ringer solution (see Fig. 1a and d). Changes in the 2nd phase are much less marked: they are not nearly so great as the increase in the rate of accommodation which occurred in the action of 2-methylnaphthaquinone or with atropine. Changes of accommodation during the action of eserine were associated with biphasic fluctuations in excitability, but the degrees of fluctuation were not the same in the 2 cases (see Fig. 2).

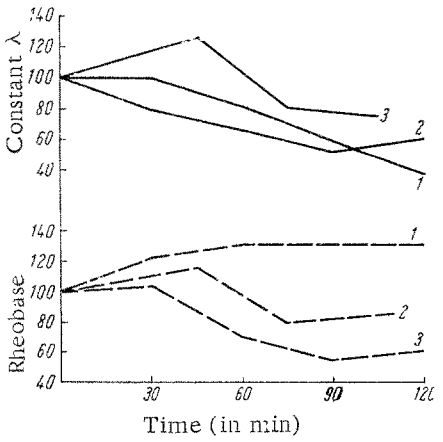

Fig. 2. Changes in the accommodation constant λ and in the rheobase in response to the action of (1) 1:10,000 2-methylnaphthaquinone, (2) 1:1,000 atropine, and (3) 1:5,000 and 1:500 eserine. Abscissa) time of action of drug in min; ordinate) accommodation constant λ and rheobase as percentage of control (mean values).

We must emphasize that all the changes in the indices of accommodation which we have described and which were evoked by various concentrations of substances which influence cholinergic transmission were statistically significant ($P \leq 0.05$), except for certain intermediate values.

The experiments in which acetylcholine acted on the nerve gave no definite results. Accommodation and rheobase changed either very little or not at all, i.e., the drug action was almost completely ineffective [3].

We must emphasize that in addition to certain general features [3] the different drugs manifested certain specific effects. Although the actual values of the initial rates of accommodation and their degree of change varied over wide limits the general tendency and the extent of the shifts which developed were closely correlated with the particular agent used. To a first approximation, in each drug we may distinguish a specific influence related to the influences produced by acetylcholine or to its metabolism. In this connection the considerable and progressive increase in the rate of accommodation under the influence of 2-methylnaphthaquinone and atropine may be interpreted as a result of a genuine influence exerted by these substances superimposed upon a more or less complete blockage of the action of acetylcholine. Under the influence of eserine, the initial effects which preponderate are due to the stabilization of acetylcholine, with the result that the rate of accommodation is reduced. On the other hand, later the direct influence of the substance becomes effective and the rate of accommodation increases. The influence of acetylcholine in the 2nd phase shows up as a restraint upon the extent of this increase. The reason why acethlcholine is relatively ineffective when applied directly appears to be due to the limited degree of permeability of the nerve to this substance [4].

Pharmacological analysis has confirmed the idea which we have previously put forward [1] that acetylcholine plays a definite part in the changes in the accommodation of nervous tissue, and that it constitutes one of the physiological factors regulating this process. Apparently it restrains the increase in the rate of accommodation in a nerve which is undergoing a modification of its properties, reducing the rate towards a more normal value. In our opinion this action of acetylcholine on accommodation is of great physiological significance: by facilitating and accelerating the changeover from local excitation to the spread of an impulse it may constitute one of the mechanisms of synaptic facilitation and summation.

SUMMARY

Drugs (2-methylnaphthaquinone, atropine, and eserine) which alter the metabolism and action of acetylcholine cause specific changes in the rate of accommodation of the frog sciatic nerve, changes which vary in their extent and in their direction. The results obtained confirm the opinion we expressed previously that acetylcholine is concerned in the changes occurring in nervous tissue during accommodation.

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