THE EFFECT OF GANGLIOBLOCKING AGENTS ON AFTER-DISCHARGES

D. A. Kharkevich

Laboratory of Specific Pharmacology of the AMN SSSR Institute of Pharmacology and Chemotherapy and the Department of Pharmacology of the I. M. Sechenov Order of Lenin 1st Moscow Medical Institute (Head of Laboratory and Department—V. V. Zakusov, Active Member of the AMN SSSR)

(Presented by V. V. Zakusov, Active Member of the AMN SSSR)

Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 49, No. 6, pp. 62-66, June, 1960

Original article submitted May 8, 1959

The investigations of V. V. Zakusov and co-workers have established that substances which inhibit synaptic conduction in the central nervous system reduce the force and shorten the duration of after-discharges connected with precedent stimulation of the afferent and pyramidal tracts [3, 4].

These data and the fact that sequential processes play an important part in the activity of the whole nervous system prompted us to investigate the effect of ganglioblocking substances on after-discharge in the sympathetic ganglia. In the literature available to us, we could find no investigations especially concerned with this question.

After-discharges in the sympathetic ganglia are most apparent after brief (1-2 seconds) stimulation of the preganglionic fibers by stimuli 50-130 per second in frequency. One can observe a particularly pronounced and prolonged after-effect with the preliminary administration of physostigmine [8, 9].

The mechanism of development of after-discharges in the sympathetic ganglia is a particularly interesting question. After-discharge in a ganglion cannot be explained by time dispersion, because the general route between the stimulating and receiving electrodes is the same for all the fibers, and the difference in the rates of conduction and synaptic lag is not great enough to explain a persistent after-effect. D. Bronk and M. Larrabee [7] observed after-discharges when action potentials were led off from single postganglionic fibers of the stellate ganglion. On this ground, one can assume that after-discharges are connected with changes developing in the bodies of the ganglionic neurons or in the presynaptic endings. In the autonomic ganglia, after-discharge is evidently caused by continuing stimulation of the ganglionic cells due to liberation of chemical substances (acetylcholine, potassium ions) persisting after tetanus has ceased [6, 8-10]. The increased frequency and duration of after-discharges following the use of eserine, or in the case of a surplus of potassium ions or a deficiency of calcium ions, or with acetylcholine perfusions of the ganglion gives this theory considerable support.

METHOD

The experiments were performed on the stellate ganglion of cats anesthetized with chloralose (80 mg/kg intravenously) and urethan (0.5-1 g per animal intravenously). The thoracic cavity was opened from the 1st to the 6th-7th rib, under conditions of artificial respiration. The preganglionic trunk was transected at the level of the 5th-6th thoracic sympathetic ganglia, and stimulating electrodes were placed between the 2nd and 3rd or the 3rd and 4th rami communicantes. The bio-electric currents were led off from the inferior cardiac nerve, transsected 3-4 cm from the ganglion. All the other postganglionic fibers and the 1st-6th ramus communicans were transected. The blood supply of the ganglion was left intact.

The preganglionic trunk was stimulated with supramaximal square-wave stimuli given at a rate of 100 per second to induce tetanus lasting one second. The duration of each stimulus was 0.1-0.5 millisecond.

The experiments were performed on a background of physostigmine (2-5 mg/kg) in order to intensify and prolong the after-effect. The ganglioblocking substances tested were tetraethylammonium (TEA), Hexonium (hexamethonium), Pentamine (methyliminodiethylene bis ethyldimethyl ammonium bromide) and Mekamine. All the substances were introduced into the femoral vein. The ganglioblocking agents were used in doses of 0.5-2 mg/kg.

RESULTS

The experiments showed a marked decrease in the after-effect after the administration of TEA in a dose of 0.5 mg/kg. This was particularly apparent after the use of the substance in a dose of 1-2 mg/kg. Figure 1, 1, for example, shows that tetanic stimulation of the preganglionic sympathetic trunk following the intravenous injection of physostigmine (3 mg/kg) was attended by a prolonged after-effect. The size of the individual discharges reached 50-60 μv. In a dose of 1 mg/kg, TEA (see Fig. 1, 2) almost completely prevented the development of the after-effect. At the same time, adequate conduction of nerve

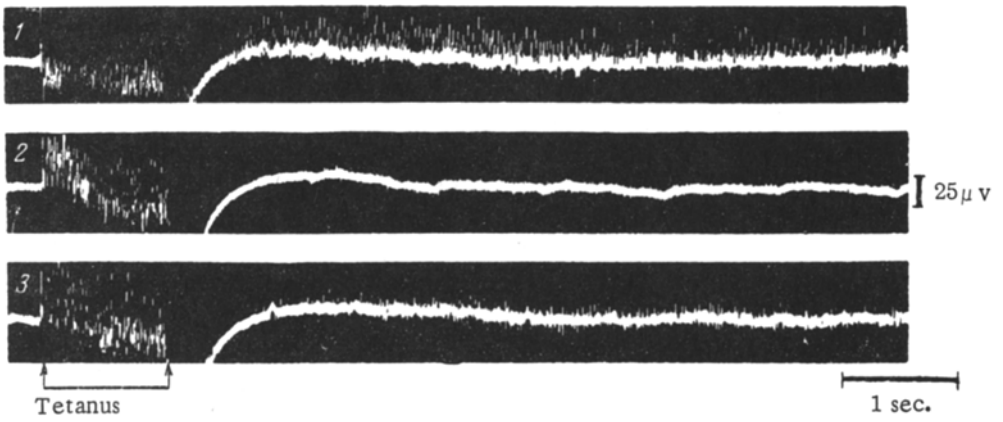

Fig. 1. Effect of tetraethylammonium on after-discharge in the stellate ganglion. 1) before administration of substance; 2) one minute after TEA injection (1 mg/kg); 3) 15 minutes after injection. Tetanus (beginning and end indicated by arrows); maximal square-wave stimuli lasting 0.5 millisecond each and given at a rate of 100 stimuli per second. Tetanic stimulation of the preganglionic fibers accomplished in one second. Experiment carried out on a background of the action of physostigmine (3 mg/kg).

impulses was retained in the ganglion. This was indicated by the pronounced potentials of the postganglionic fibers which were observed during the tetanus. Under the given experimental conditions, it was difficult to record their true value, because the experiments required maximal amplification of the action potentials. This was necessary in order to study the after-discharges, which usually ranged from 10 to 30 μv in value. Naturally, the potentials of the postganglionic fibers, which reached amplitudes of 500-700 μv (with electric stimulation of the preganglionic trunk), often exceeded the limits of the screen.

Fig. 1, 3 shows a tendency of the after-effect to reappear. After the use of TEA, due to the brevity of its effect, the complete restoration of the value and duration of the after-discharge could be easily observed.

Analogous results were obtained with Hexonium, Pentamine and Mekamine. In a dose of 1-2 mg/kg, all these substances prevented the development of after-discharges. The effect lasted longer than that produced by the TEA injection. The most lasting effect was induced by Mekamine. With regard to duration of effect, the ability of the experimental ganglioblocking agents to inhibit the after-discharge was parallel to their inhibitory influence on the interneuronal conduction of nerve impulses.

Fig. 2 shows the results of one of the experiments with Mekamine. The experiment was performed on a background of physostigmine (3 mg/kg intravenously). The top oscillogram (see Fig. 2, 1) shows brief tetanus (100 stimuli per second for 1 second) attended by a marked after-effect. Mekamine was given in two injections of 1 mg/kg each. After the first injection of the substance (see Fig. 2, 2), we noted a sharp decrease in the duration and amplitude of the after-discharges, which were observed only during the first $2\frac{1}{2}$-3 seconds after tetanus. The second injection of 1 mg/kg Mekamine (see Fig. 2, 3) caused the after-discharges to decrease still further in voltage; no after-discharges were observed after the first $1\frac{1}{2}$ seconds following tetanus.

As well as the ganglioblocking agents, we tested substances from other pharmacological groups (Barbamyl and Novocain). Both these compounds are known to inhibit the autonomic ganglia quite actively. The results of these experiments demonstrated that the effect of Barbamyl or Novocain on the after-discharge is similar to that of the ganglioblocking substances. We observed the decrease or complete inhibition of the after-discharges after the administration of 20-30 mg/kg Novocain or 15-20 mg/kg Barbamyl. This effect developed considerably earlier than did the block of ganglionic transmission in this case.

The results of the experiments indicate that the experimental ganglioblocking agents reduce or completely prevent the development of after-discharges. This effect was usually attended by a decrease in the amplitude of the bio-electric currents in the tetanic series. Complete block of ganglionic transmission did not occur in this case. Therefore, the ganglioblocking substances primarily prevent the development of the after-effect, but higher doses are required before they can block the conduction of nervous excitation in the ganglion with electric stimulation of the preganglionic fibers.

The action mechanism of the experimental substances seems to be based on their ability to inhibit the synaptic apparatuses of the ganglionic neurons, at the same time increasing the latter's threshold of sensitivity to acetylcholine. However, one should take into account the fact that certain substances (Novocain) can decrease the production of acetylcholine. It is interesting that the parameters characterizing the function of the neurons and of their syn-

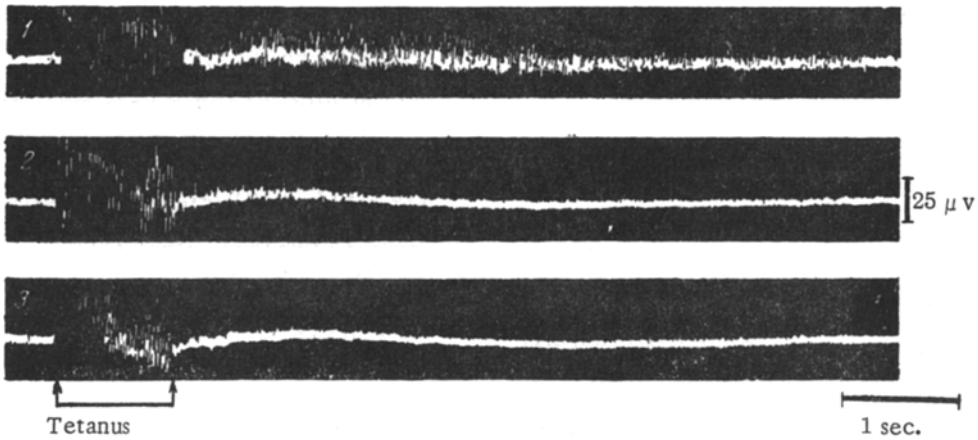

Fig. 2. Effect of Mekamine on after-discharge in the stellate ganglion. 1) before administration of substance; 2) five minutes after Mekamine injection (1 mg/kg); 3) five minutes after second Mekamine injection (1 mg/kg). Other symbols the same as in Fig. 1.

aptic formations change in about the same way under the influence of ganglioblocking agents. Thus, for example, we have shown that ganglioblocking substances, as well as reducing the excitability of the ganglia, decrease their functional mobility, increase the time of interneuronal conduction and, as established in this investigation, diminish and abbreviate the after-discharge.

This brings up the question of how these functional characteristics would change under the influence of other substances capable of inhibiting ganglionic transmission by various mechanisms of action. We used Barbamyl and Novocain for purposes of comparison. It was found that both substances caused the same changes in the excitability, lability, latent period and after-discharges of the sympathetic ganglia as did the experimental ganglioblocking agents.

On the basis of these data, one can assume that other substances which inhibit synaptic conduction in the autonomic ganglia ought to induce analogous effects. However, in evaluating the common principles of action of ganglioblocking agents, one should remember that the changes which lead to disturbance of ganglionic transmission may be brought about by very different mechanisms. This also applies to the anatomical localization of the effect of ganglioblocking agents and to the influence of these substances on the biochemical processes important to the transmission of nervous excitation. For example, Z. Zaimis and co-workers [5] believe Mekamine and Hexonium to have different mechanisms of action. These authors associate Mekamine's blocking effect with its intracellular action; Hexonium, on the other hand, affects the synaptic formations of the ganglionic neurons.

N. V. Vysotskaya [1, 2] established in our laboratory essential differences as to the type of effect exerted by ganglioblocking agents on certain aspects of metabolism. Investigation of the metabolism of the phosphorus groups in the superior cervical ganglion showed that nicotine, pachycarpine, TEA and Pentamine reduce the content of adenosine triphosphoric acid (ATP) in the ganglion; Hexonium is not active in this respect. The fact that ATP restores conduction of stimulation in the ganglion if the conduction has been inhibited by nicotine, pachycarpine, TEA or Pentamine indicates that the change in the ATP content plays an important part in the action mechanism of most of the experimental ganglioblocking agents. The blocking effect of Hexonium does not change under the influence of ATP. One must therefore suppose that the mechanism of Hexonium's blocking effect differs from that of Pentamine and TEA. According to the classification of W. Paton, W. Perry and co-workers, however, these substances all belong to the competitively acting groups of compounds [11, 12].

Therefore, with the aid of the physiological parameters characterizing the interneuronal transmission of nervous stimulation, we were able to obtain an idea of the general outlines of the action of ganglioblocking agents. To gain a more intimate understanding of the mechanism of their depriming effect, the biochemical or physicochemical changes of the synaptic formations and of the nerve cells as a whole should evidently be investigated.

SUMMARY

The author studied the effect of tetraethylammonium, Hexonium, Pentamine, Mekamine, Barbamyl and Novocain on the after-discharges in the cat's stellate ganglion. As demonstrated by the experimental results, all these substances reduce or completely inhibit the development of after-discharges. This action is accompanied by a decrease in the amplitude of the action potentials in the tetanic series during electric stimulation of the preganglionic fibers; but complete block of the ganglionic transmission does not occur.

LITERATURE CITED

1. N. B. Vysotskaya, Farmakol. i Toksikol. 20, 2, 12-15 (1957).*
2. N. B. Vysotskaya, Farmakol. i Toksikol. 20, 4, 3-7 (1957).*
3. V. V. Zakusov, Fiziol. Zhur. SSSR 36, 2, 184-190 (1950).
4. N. A. Kruglov, The Effect of Anesthetic Substances on the Liability and Certain Other Functional Properties of the Nerve Center. Author's Abstract of Candidate's Dissertation [in Russian] (Leningrad, 1955).
5. G. Bennett, C. Taylor, E. Zaimis, Lancet 2, 218-222 (1957).
6. D. W. Bronk, J. Neurophysiol. 2, 380-401 (1939).
7. D. W. Bronk, M. G. Larrabee, Fed. Proc. 5, 60-61 (1946).
8. J. C. Eccles, J. Physiol. 103, 27-54 (1944).
9. J. C. Eccles, The Neurophysiological Basis of Mind (New York, 1953).
10. No. R. de Lorente, Am. J. Physiol 121, 331-349 (1958).
11. W. D. M. Paton, W. L. M. Perry, J. Physiol. 119, 43-57 (1953).
12. W. L. M. Perry, J. Talesnik, J. Physiol. 455-469 (1953).

*See C. B. translation.