THE EFFECT OF GANGLIOBLOCKING AGENTS ON SYNAPTIC TRANSMISSION OF NERVOUS EXCITATION IN THE SYMPATHETIC GANGLIA

D. A. Kharkevich

Department of Pharmacology of the 1st Moscow Order of Lenin I. M. Sechenov Medical Institute and the Laboratory of Specific Pharmacology of the AMN SSSR Institute of Pharmacoloy and Chemotherapy (Head of Department and Laboratory – Active Member AMN SSSR Professor V. V. Zakusov), Moscow
(Presented by Active Member AMN SSSR V. V. Zakusov)
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Study of the action mechanism of ganglioblocking agents has shown that Hexonium, Mekamine,* and Pentamine depress or prevent the development of post-activation facilitation in the stellate ganglion, but that tetraethylammonium does not [1]. On the basis of these data, I assumed that the first three substances act on the presynaptic endings. This assumption was confirmed by experiments in which acetylcholine was intraarterially introduced toward the ganglion and the antidromic discharges in the preganglionic fibers were recorded [3]. The potentials disappeared in both the post- and preganglionic fibers after the use of Hexonium. It is evident from these data that Hexonium has an inhibitory effect on the terminal ramifications of the preganglionic axons. I obtained analogous results with Pentamine, Mekamine, and tetraethylammonium.

Therefore, ganglioblocking preparations can disturb the function of the presynaptic endings, as well as block the n-cholinergic structures of the ganglion.

To find the precise site of ganglioblocking agents' effects, however, one must know whether postsynaptic neuronal conduction of excitation is affected by these substances. For this purpose, changes developing in the postsynaptic ganglionic neurons (excluding the subsynaptic membrane and n-cholinergic structures) must be differentiated from disturbances of the n-cholinergic structures.

EXPERIMENTAL METHODS

I used "post-activation" (post-tetanic) inhibition [2] to study the effect of ganglioblocking agents on the functional state of postsynaptic neurons; I also determined the bioelectric activity of the ganglionic cells during antidromic stimulation.

The first parameter was chosen because post-activation inhibition is post-synaptic in origin, resulting from the meeting in the same neurons of two excitation waves traveling along different synaptic pathways.

Experiments were performed on anesthetized cats (80 mg/kg chloralose and 0.5-1 g urethan, intravenously). The thoracic cavity was laid open (from rib I to rib VII) under conditions of artificial respiration. The preganglionic trunk (at the level of the V-VI thoracic sympathetic ganglia), the postganglionic fibers, and all the rami communicantes were transected. The ganglionic blood supply was left intact. Bipolar, platinum electrodes were placed on the inferior cardiac nerve, which was transected 3-4 cm from the stellate ganglion. One stimulating electrode (P_2) was placed on the sympathetic chain at the level of the III-IV thoracic ganglia; a second (P_1), usually on the third ramus communicans (Fig. 1A).

The order of the experiments was as follows. Stimulation by single, supramaximal square-wave stimuli 0.1 to 0.5 msec in duration was first applied through electrode P_1. Before tetanus, the single stimuli were given at intervals of 5-15 sec. Tetanic stimulation by electrode P_2 followed at a frequency of 30 stimuli per sec for 10-15 sec. Each stimulus lasted 0.1-0.5 msec. Five, 10, 15, 20, 30, 45, 60, 90, 120, and 150 sec after tetanus, the preganglionic fibers were again stimulated with electrode P_1. The degree of post-activation inhibition was judged from the maximal

*Name not verified – Publisher's Note.

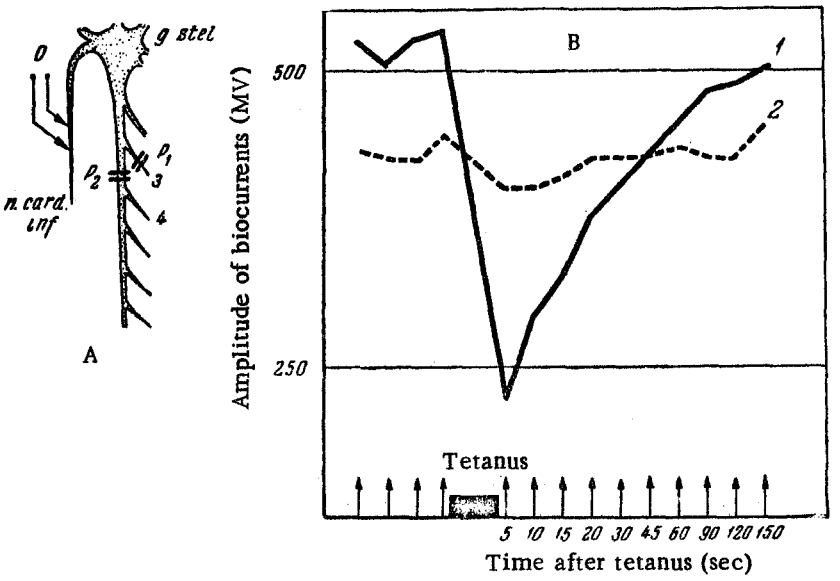

Fig. 1. Effect of Hexonium on post-activation inhibition in the stellate ganglion. A. Diagram showing positioning of electrodes; P_1 and P_2, stimulating electrodes; O, derivation electrodes. B. Amplitude of potentials in post-ganglionic fibers before (1) and one min after (2) intravenous injection of Hexonium (0.5 mg/kg). Tetanus: supramaximal square-wave stimuli 0.5 msec in duration given at a frequency of 30 per sec. Total duration of tetanus 10 sec. Vertical arrows: single, supramaximal square-wave stimulation 0.1 msec in duration. Experiment on anesthetized cats (80 mg per kg chloralose and 300 mg/kg urethan, intravenously).

decrease in amplitude of the potentials during stimulation of the preganglionic fibers by single stimuli (P_1). The single discharges evoked before and after tetanus were compared.

Hexonium, Pentamine, tetraethylammonium (TEA), and Mekamine were the experimental substances. They were administered intravenously.

EXPERIMENTAL RESULTS

In a dose of 0.4-2 mg/kg, Hexonium reduced post-activation inhibition in almost all the experiments (Fig. 1B). This was preceded by a considerable drop in the amplitude of the potentials during tetanic stimulation.

Unlike Hexonium, Pentamine (0.3-1 mg/kg) did not affect post-activation inhibition. No significant decrease in the tetanic series of potentials was observed without corresponding decrease in the biocurrents evoked by the single stimuli. The sharp decrease in amplitude of the potentials shortly after the start of tetanic stimulation observed with the use of corresponding amounts of Hexonium was not observed in the case of Pentamine.

TEA was tested in a dose of 0.3-1 mg/kg. The most suitable doses were found to be 0.3-0.5 mg/kg, which produced a rather marked decrease in the biocurrents without increasing post-tetanic inhibition. These doses of TEA had practically no effect on post-activation inhibition.

Mekamine was administered in a dose of 0.3-2 mg/kg. It either decreased or did not change post-activation inhibition. The reason for the varying effect of this drug was probably that there was a different degree of decrease in the tetanic series in different experiments. When the biocurrent decreased sharply and almost disappeared soon after stimulation started (2-3 sec), inhibition was usually weaker than in the control. With a lesser degree of change in the potentials during tetanus, no change in inhibition occurred.

Therefore, post-activation inhibition is reduced by Hexonium and, less regularly, by Mekamine; it is very little affected by Pentamine and TEA.

Post-activation inhibition, then, is directly related to the amplitude of the potentials during tetanus. If a drug like Hexonium considerably reduces the latter, inhibition is also reduced. In all probability, therefore, the reduced

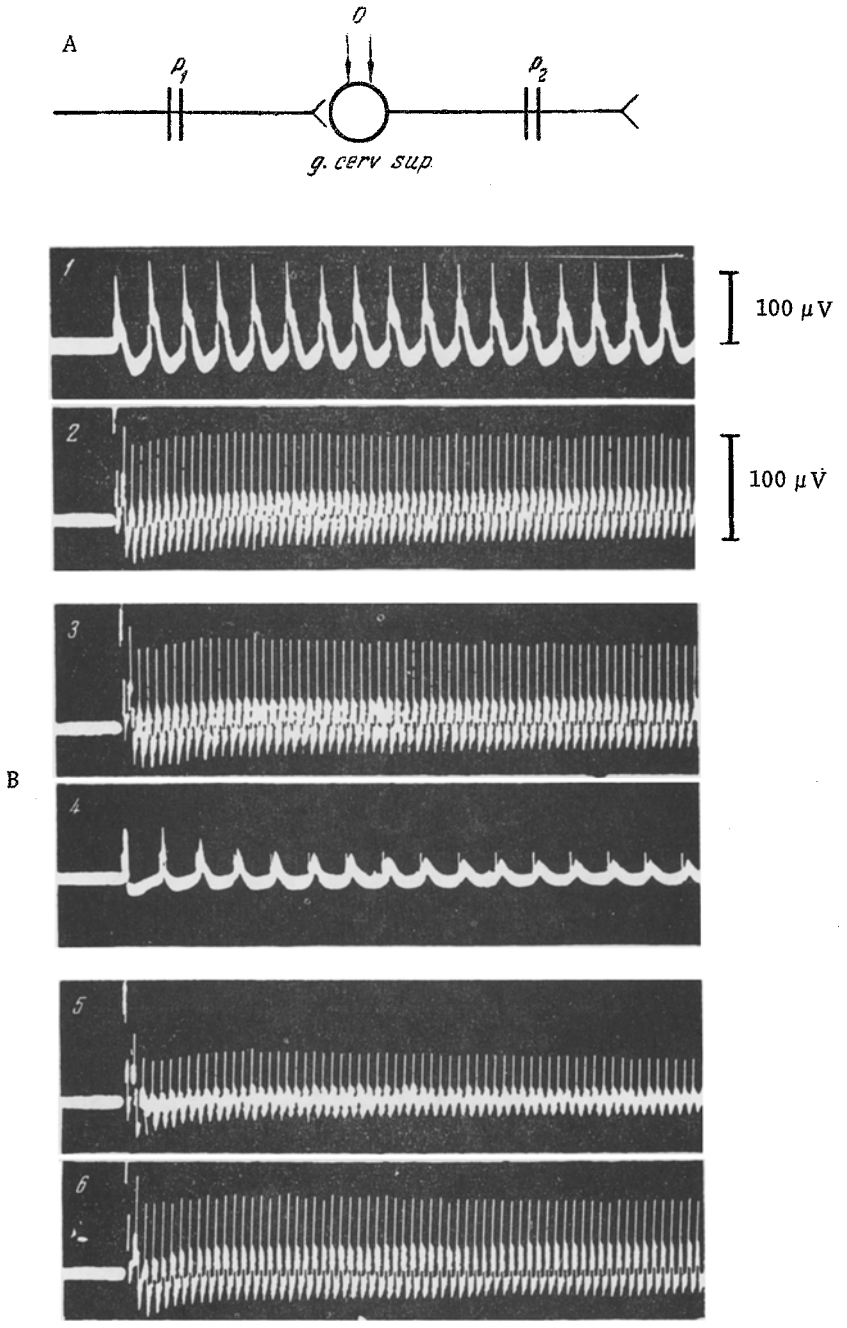

Fig. 2. Effect of Pentamine and Novocain on the bioelectric activity of the superior cervical ganglion. A. Positioning of electrodes. P_1) stimulating electrodes on preganglionic fibers; P_2) stimulating electrodes on post-anglionic fibers; O) electrodes for recording the potentials. B. Potentials of superior cervical ganglion; 1,4) with orthodromic stimulation (maximal square-wave stimuli with duration of 0.1 msec each, given at frequency of 10 per sec); 2, 3, 5,6) with antidromic stimulation (supramaximal square-wave stimuli 0.1 msec in duration and 45 per sec in frequency). 1,2) Before administration of drug; 3) 1 min after intravenous injection of Pentamine (10 mg/kg); 4) 4 min after; 5) 2 min after intravenous injection of Novocain (20 mg/kg); 6) 9 min after. Experiment on anesthetized cats (80 mg/kg chloralose and 400 mg/kg urethan, intravenously).

inhibition observed with the use of Hexonium or Mekamine is not due to any pharmacological effect on the function of the post-synaptic ganglionic neurons. It is due to the fact that the latter conduct a smaller number of impulses, so that the period required to restore excitability after the preceding activity is shorter. This was easy to verify by using different frequencies of stimulation within the same time interval. For example, when the stimulation frequency was decreased to 5-10 stimuli per sec, or increased to 100 per sec with the corresponding pessimal phenomena, post-activation inhibition was less marked than with a frequency of 30 stimuli per sec. Therefore, decrease in the number of ganglion cell discharges (during tetanic stimulation) is, up to a certain point, attended by decrease in post-tetanic inhibition.

These results give reason to believe that these gangliolytics (in the experimental doses) do not increase post-activation inhibition and apparently do not depress the functional condition of postsynaptic ganglionic neurons.

To verify this conclusion, I conducted a series of experiments with antidromic stimulation. Experiments were performed on the superior cervical and stellate ganglia. The ganglia were isolated from the central nervous system (all preganglionic fibers were transected); their blood supply was left intact. Potentials were derived directly from the body of the ganglion (Fig. 2A) by bipolar needle electrodes 75-100 microns in diameter. The post-ganglionic fibers were stimulated. For comparative purposes, I used orthodromic stimulation of the preganglionic fibers (P_1 electrodes), as well as antidromic (P_2 electrodes). Stimulation frequency ranged from 10-80 stimuli per sec, each stimulus lasting 0.1-0.5 msec. The amplitude ranged from supraliminal to supramaximal.

The experiments were performed on cats anesthetized with chloralose (80 mg/kg intravenously) and urethan (300 mg/kg intravenously). The substances were introduced into the femoral vein.

These experiments showed that none of the experimental ganglioblocking agents (in doses of 0.5-10 mg/kg) affect the level of the ganglionic potentials regardless of the amplitude or frequency of antidromic stimulation (Fig. 2B). With orthodromic stimulation, however, the biocurrents of the ganglion decreased in direct proportion to the dose of the substance. Even when transmission of nervous excitation from the pre- and post-ganglionic fibers was totally blocked, the reaction of the ganglionic cells to antidromic stimulation did not change. However, Novocain in doses of 20-30 mg/kg (intravenously) caused a definite decrease in the antidromic discharges.

Therefore, the results of all the experiments conducted clearly indicate that the experimental gangliolytics do not affect conduction of excitation in post-synaptic ganglionic neurons. Consequently, the mechanism of their inhibitory effect must consist primarily in reducing the excitability of the n-cholinergic structures, with functional inhibition of the pre-synaptic terminals.

SUMMARY

A study was made of the effect produced by the ganglioblocking substances tetraethylammonium, Hexonium, Pentamine, and Mekamine, on the post-activating inhibition in the sympathetic ganglia and the bioelectric activity of the ganglia in antidromic conduction of excitation. None of the substances tested increased the post-activating inhibition or disturbed the antidromic conduction along the post-synaptic neurones. As distinct from the ganglioblocking substances, Procaine produced a depressive effect on the functional state of the post-synaptic part of the ganglionic neurones. Consequently, disturbance of the interneurone transmission of excitation in the autonomic ganglia occurring under the effect of ganglioblocking substances is largely connected with the reduced excitability of the ganglion cholinoceptors, but may evidently also depend on the depressive gangliolytic effect on the activity of presynaptic terminals.

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