SENSITIZATION OF THE SUPERIOR CERVICAL SYMPATHETIC GANGLION TO THE ACTION OF MEDIATORS BY PROCAINE AND XYLOCAINE

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We have previously reported [6, 7, 9] on the ability of local anesthetics to inhibit the development of effects of excitation in ganglia caused by inadequate (induction current) and adequate (chemical factors of synaptic transmission) stimuli. In most experiments the doses of the latter were 10-20 μg. In the present paper we describe the results of experiments in which changes of a different pattern were revealed in the functional state of a sympathetic ganglion when acted upon by extremely small doses of mediators and local anesthetics.

METHOD

The superior cervical sympathetic ganglion of a cat was perfused [1] with Ringer–Locke solution without the addition of eserine. The reactions of the effector organ–the nictitating membrane–were recorded. In the course of the experiment the effects of only one mediator (acetylcholine or histamine) and of one local anesthetic (procaine or xylocaine–the latter manufactured by the firm of Astra) were investigated. At the beginning of the experiment the threshold (and sometimes, the superthreshold) dose of mediator was determined. Injection of threshold doses was repeated 2-3 times; as soon as a reaction of the nictitating membrane of constant magnitude was obtained, the injection of test doses (also repeated 2-3 times) of the mediators was begun. Immediately thereafter, the same test dose of mediator was applied to the ganglion together with the local anesthetic or 20-25 sec after injection of the latter. At the end of the reaction of the nictitating membrane mediator alone was again injected in the same dose. The method is described in detail in our previous communications [6, 7, 9].

RESULTS

Besides many other facts previously observed [7, 9], the experiments again confirmed (in agreement with data in the literature) that histamine gives rise to phenomena of excitation in the sympathetic ganglion of the same order as those caused by acetylcholine, and sometimes of a higher order. In most experiments the local anesthetics were administered to the ganglion in doses of only 1/500 to ½ the dose of mediator. Under these circumstances the dose of mediator was of the order of one millionth or one ten-millionth of one gram.

When such infinitesimally small doses of mediators were applied to the synapses simultaneously with the local anesthetics, or after an interval of 20-25 sec, the anesthetics did not exhibit their antimediator action accompanying neurotomy. On the contrary, in this case a phenomenon of the opposite character was found. For example, the reaction of contraction of the nictitating membrane to acetylcholine or histamine [7], injected simultaneously with procaine, was increased considerably, not only in amplitude, but also in duration, indicating an increase in the strength of excitation in the ganglion.

In a series of experiments increasing responses of the nictitating membrane to a single simultaneous (or separated by an interval of 20-25 sec) administration of anesthetic and mediator continued to take place, even during a series of successive administrations of mediator alone (in the same doses), and only gradually resumed their original magnitude. In the experiment illustrated in Fig. 1, the amplitude of the contraction of the smooth muscle of the

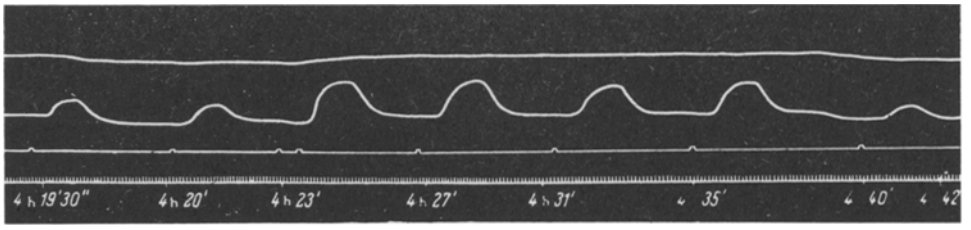

Fig. 1. Sensitization of the superior cervical sympathetic ganglion to acetylcholine by procaine. Perfusion of right ganglion. Significance of the curves from top to bottom: reaction of nictitating membrane on the left side, reaction of nictitating membrane on the right side; marked of time of injection of drug; time marker (5 sec). From left to right: two injections of acetylcholine in a dose of 0.25 μg; injection of the same dose of acetylcholine 25 sec after injection of procaine in a dose of 0.0125 μg; four injections of acetylcholine alone in a dose of 0.25 μg.

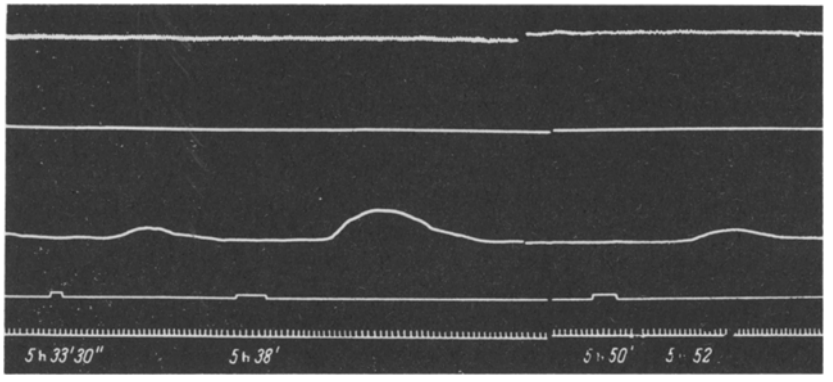

Fig. 2. Sensitization of the superior cervical sympathetic ganglion to acetylcholine by xylocaine. Perfusion of right ganglion. Top curve—respiration. Significance of remaining curves as in Fig. 1. From left to right: injection of acetylcholine in a dose of 1 μg; injection of the same dose of acetylcholine together with xylocaine in a dose of 0.0125 μg; injection of acetylcholine alone in a dose of 1 μg.

nictitating membrane rose by 123% in relation to its initial magnitude. Besides this increase in the reaction of the nictitating membrane on the same side as the injection, a slight increase in the tone of the nictitating membrane on the opposite side was also observed.

A completely similar result was observed when the other local anesthetic—xylocaine—was applied to the synapses of the ganglion along with acetylcholine (Fig. 2) or with histamine (Fig. 3). In the latter case the effect of contraction of the nictitating membrane increased in amplitude by 270% and in duration by 77% over the initial value. Hence, infinitesimally small doses of local anesthetics not only did not inhibit the development of excitation in the ganglion following application of acetylcholine and histamine to its synapses, but, on the contrary, had the opposite effect—they increased the sensitivity of the ganglion, i.e., sensitized it to the action of the mediators. These facts have not been described in the literature.

It should be noted that in a series of experiments, as the doses of anesthetics injected into the flow of perfusion fluid increased, their sensitizing influence was observed to give way to antimediator effects (the doses of mediator being unchanged). In this way a point of transition of the state of excitation of the ganglion into a state of inhibition could be identified, demonstrating the phased character of the action of these local anesthetics. In one experiment, for instance, xylocaine in a dose of 1 μg (or less) sensitized the ganglion to a dose of histamine of 0.1 μg, whereas xylocaine in a dose of 2.5 μg produced a reversible inhibition of the effect of the same dose of histamine (Fig. 3).

Comparison of the results of the action of small and large doses of mediators on the ganglion further showed that the dose of mediator applied to the synapses of the ganglion may also largely determine the initial level of

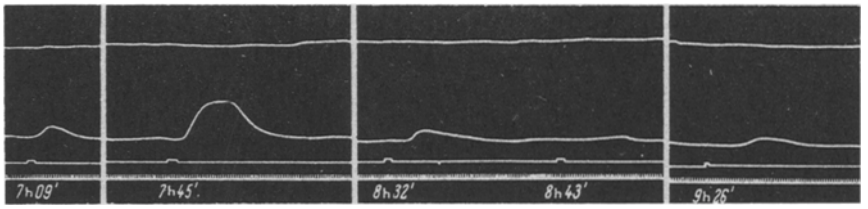

Fig. 3. Sensitization of superior cervical sympathetic ganglion to histamine by xylocaine. Perfusion of the right ganglion. Significance of the curves the same as in Fig. 1. From left to right: injection of histamine in a dose of 0.1 μg; injection of the same dose of histamine together with xylocaine in a dose of 1 μg; injection of histamine alone in a dose of 0.1 μg; injection of the same dose of histamine together with xylocaine in a dose of 2.5 μg; injection of histamine along in a dose of 0.1 μg.

excitability of the ganglion, i.e., its initial functional state. The latter, in turn, determines the character of the observed effects of the local anesthetics.

Results demonstrating the same relationship in principle between the character of the effect of adrenalin and the doses of acetylcholine have been reported by K. M. Bykov and V. S. Sheveleva. Adrenalin stimulates oxidation-reduction processes and metabolism in the ganglion [5, 12] and sensitizes the ganglion to small doses of acetylcholine [2]. It has also been shown that procaine [3, 4, 10, 11, 15] and xylocaine [13] stimulate metabolic processes, including oxidation-reduction processes, in the body. The extensive literature describing the beneficial results of the use of procaine in gerontology and geriatrics must also be taken into consideration.

From a comparison of these results with the experimental data described above, it may be concluded that the character of the action of both procaine and xylocaine, on the one hand, and of adrenalin, on the other, is nonspecific. It is clear that the analogy observed between the effects of these substances is not limited to their purely phenomenological similarity, but is determined by their possession of common chemical mechanisms, producing the effect of sensitization.

The phenomenon of the sensitization of various structures to the action of different factors, as described by many writers [12, 14], is a widespread biological phenomenon. There are grounds for regarding it as one of the forms of nonspecific reaction of a physiological system to adequate and inadequate stimulation. The importance of the phenomenon of sensitization to the body is shown up in greater detail when it is considered in the broad framework of the biological principles governing the mobilization of the reserve powers of the organism and the operation of trophic influences.

As these experiments show, both local anesthetics—procaine and xylocaine—possess common substances which exert an antimediator action and which are capable of causing, within a range of doses of the order of one ten-millionth of a gram or less, effects of a different character—sensitizing influences on nerve structures. The discovery of the phased character of the action of procaine and xylocaine when applied to the synapses of the ganglion confirms the analogous conclusions drawn from experiments in which these substances were injected into the blood stream [18].

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. ***Some or all of this periodical literature may well be available in English translation.*** **A complete list of the cover-to-cover English translations appears at the back of this issue.**
