EFFECT OF MEDIATORS AND ANESTHETICS ON THE FUNCTIONAL STATE OF THE SUPERIOR CERVICAL SYMPATHETIC GANGLION

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 56, No. 11, pp. 89-93, November, 1963
Original article submitted June 12, 1962

The object of this investigation was to study experimentally the action of various doses of acetylcholine and also of histamine, which also possesses a mediator function [10, 21, 28, 30], on the ganglion, and also to determine the action of anesthetics (novocain, diethylaminoethanol, and xylocaine) on the effects produced by these adequate stimuli.

EXPERIMENTAL METHOD

The superior cervical sympathetic ganglion of a cat was perfused [5] with Ringer-Locke solution without the addition of eserine. In one experiment the effects of acetylcholine alone or of histamine alone, in the form of their hydrochlorines, were studied. Novocain, diethylaminoethanol, and xylocaine (Astra) were applied to the ganglion together with the mediators or 10-20 sec before administration of the latter. The changes in the functional state of the ganglion were judged by the reaction of an effector organ – the nictitating membrane – recorded on a kymograph. The reactions of the opposite nictitating membrane were recorded at the same time. The method is described in detail in previous communications [15, 16].

EXPERIMENTAL RESULTS

In doses of the order of 0.1 μg of acetylcholine caused excitation of the sympathetic ganglia, in agreement with results obtained by other workers [19, 25].

With an increase in the dose of acetylcholine its effects diminished or completely disappeared, in agreement with observations made on various test objects [4, 7, 9, 11]. According to the theories of N. E. Vvedenskii and other authors [7, 9], these results may be explained by the conversion of excitation into inhibition.

Like acetylcholine, histamine caused excitation in a dose of 0.005 μg, whereas doses of the order of 0.01 μg caused a contraction reaction of the nictitating membrane of considerable amplitude and duration. Histamine also gave rise to biphasic reactions. It caused changes in the functional state of the superior cervical sympathetic ganglion, and the strength of its physiological effect was not inferior, and in some cases was actually superior, to that of acetylcholine.

The effect of anesthetics in the transmission of excitation produced in the sympathetic ganglion by electrical stimulation has been studied previously [16]. In the present study it was important to investigate their effect during the action of chemical factors of synaptic transmission (acetylcholine, histamine) on the ganglion. Whereas it was previously found that novocain reversibly abolishes the effects of the mediator in doses greatly in excess of the latter [14, 27], the present study showed that these antimediator effects of novocain may be observed when the relative doses of mediator and novocain are varied – when, for example, the dose of novocain is many times less than that of the mediator. For instance, in the experiment illustrated in Fig. 1, a the dose of novocain was only 1/1600 of the dose of mediator, yet the antiacetylcholine action of novocain was clearly seen. The combined administration of novocain and acetylcholine to the ganglion in the perfusion medium caused a reversible decrease in the amplitude of the contraction of the cat's nictitating membrane by comparison with the contraction caused by acetylcholine alone. It is interesting to note that an antimediator effect was observed when a product of the hydrolysis of novocain in the body – diethylaminoethanol – was administered to the ganglion together with the mediator (Fig. 1, b).

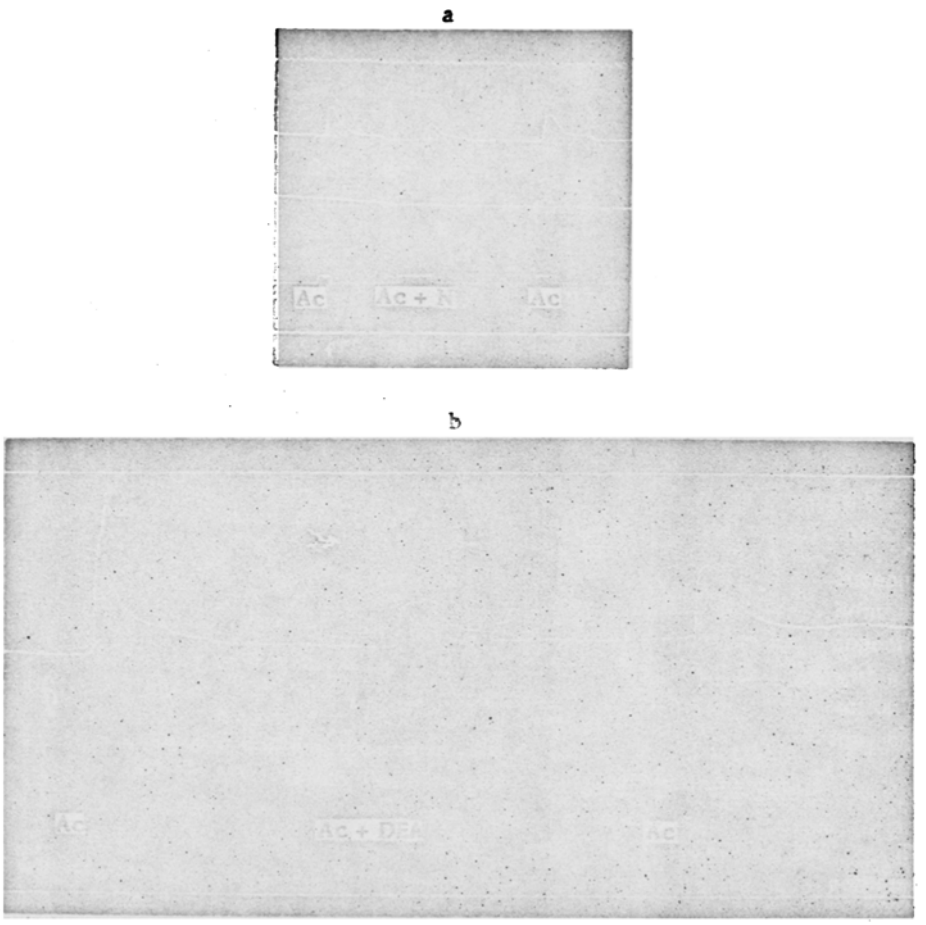

Fig. 1. Perfusion of the superior cervical sympathetic ganglion. A) Left ganglion. Significance of the curves (from above down): respiration; reactions of the left nictitating membrane; reactions of the right nictitating membrane; marker of moment of injection of drug; time marker (5 sec); from left to right; injection of acetylcholine (Ac) in a dose of 20 μg; injection of the same dose of acetylcholine together with novocain (N) in a dose of 0.0125 μg; injection of acetylcholine in a dose of 20 μg; b) right ganglion. Significance of curves (from above down): reactions of left nictitating membrane; reactions of right nictitating membrane; time marker (5 sec); the arrows indicate the time of injection of the drugs. From left to right: injection of acetylcholine in a dose of 10 μg; injection of the same dose of acetylcholine together with diethylaminoethanol (DEA) in a dose of 10 μg; injection of acetylcholine in a dose of 10 μg. The latent periods of the reactions of the nictitating membrane are underlined.

As regards the speed, strength, and duration of its anesthetic action, xylocaine considerably surpasses novocain [16]. We discovered that xylocaine possesses an antiacetylcholine (Fig. 2) and an antihistamine (Fig. 3) action. These effects were clearly defined when xylocaine (like novocain) was used in doses many times smaller than the doses of the mediators. Xylocaine had a well-marked antihistamine effect: the contraction reactions of the nictitating membrane were still not restored to their initial amplitude 48 min after application of 0.05 μg xylocaine to the ganglion (Fig. 3). In some cases the latent period of the reaction of the nictitating membrane in response to mediator applied to the ganglion along with one of the three anesthetics mentioned above was also lengthened (see Fig. 1, b).

The antimediator action of xylocaine has been inadequately explained. There are reports in the literature of the antiacetylcholine (atropine-like) properties of xylocaine and of its antinicotine action. It has been suggested that the mechanism of action of xylocaine is not associated with biologically-like substances such as acetylcholine, histamine, and so on, in contrast to novocain and other anesthetics [31].

Fig. 2. Perfusion of the left superior cervical sympathetic ganglion. Significance of the curves (from above down): respiration; reaction of the left nictitating membrane; marker of time of injection of drugs; time marker (5 sec). From left to right; injection of acetylcholine (Ac) in a dose of 20 μg; injection of the same dose of acetylcholine together with xylocaine (X) in a dose of 0.0125 μg; injection of acetylcholine in a dose of 20 μg, injection of acetylcholine in a dose of 20 μg.

Fig. 3. Perfusion of the right superior cervical sympathetic ganglion. Significance of the curves as in Fig. 2. From left to right: injection of histamine (H) in a dose of 0.5 μg; injection of histamine in a dose of 5 μg; injection of histamine in the same dose; injection of the same dose of histamine together with xylocaine (X) in a dose of 0.05 μg; injection of histamine in a dose of 5 μg; injection of histamine in the same dose.

Hence, as a result of the antimediator action of the three substances investigated, a reversible depression or complete suppression of the reaction of the effector organ took place. The results demonstrate that these anesthetics influence the chemical factors of synaptic transmission.

It may be concluded from the numerous experimental and clinical observations that acetylcholine and histamine in certain conditions possess the properties of the chemical pain mediators [3, 24, 29]. It has also been stated that these substances are concerned in the production of shock, allergic, and other states [2, 12].

Meanwhile, it is widely known that novocain can be used for the relief of pain and certain toxic conditions, for the prevention and treatment of shock, and as an antiallergic substance [6, 18]. The parallelism between the ability of novocain to exert a local-anesthetic action and to depress the effects of acetylcholine and histamine has been noted in several papers dealing, not only with the sympathetic ganglion [14, 27], but also with other objects [1, 8, 20, 23]. Reports have also been published of the anesthetic properties of diethylaminoethanol [22] and xylocaine [13, 16, 31].

Hence these anesthetics, with their antimediator action, are highly effective in the treatment of various diseases the development of which is associated with acetylcholine and histamine.

The results show that the anesthetics which were investigated possess common properties in relation to mediators. It appears that the use of these substances to relieve pain and other pathological states is based on their ability to depress the action of mediators.

Novocain and xylocaine have also revealed certain properties with a common trend when injected into the blood stream [17]. In this connection it is interesting to note that a wide range of substances possessing anesthetic properties also possess other common properties – antifibrillatory, spasmolytic, lowering the body temperature, and so on [4]. The explanation of this phenomenon is that all these substances depress the effects produced by acetylcholine [8, 23, 27].

A relationship has also been established between anesthetic and antihistamine activity [20, 26].

These facts, in Burn's opinion [4], provide a general basis for the understanding of the similarity which exists between these substances. The experiments described above provide an experimental interpretation of one aspect of the mechanism of action of anesthetics, aimed at the relief of various pathological states.

SUMMARY

In experiments with perfusion of the superior cervical sympathetic ganglion of warm-blooded animals a study was made of the effect produced by mediators on the functional state of the ganglion and their modification by anesthetics (novocain, diethylaminoethanol, xylocaine). The anesthetics under study had some common properties – they inhibited ganglion excitation (provoked not only by acetylcholine, but also by histamine), even in doses hundreds of times below the mediator doses. The results obtained help to explain the wide therapeutic use of anesthetics in various pathological states by the fact that these agents possess an antimediator effect.

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