EFFECT OF TRIMETHYLAMMONIUM IODIDE AND TRIMETHYLAMINE HYDROCHLORIDE ON POSTGANGLIONIC SYMPATHETIC NERVE FIBERS

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The nicotine-like compound tetramethylammonium iodide (TMA) and trimethylamine hydrochloride (TRIMA) depress the responses of the nictitating membrane to stimulation of the postganglionic cervical sympathetic nerve. This effect is due to the sympatholytic activity of the compounds, which is approximately ten times greater for TMA than for TRIMA.

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A structural component of bretylium, xylocholine, and other sympatholytics is quaternary (ammonium) nitrogen, conversion of which into tertiary leads to loss of activity of these compounds [1, 4, 13, 15, 16]. In this way the sympatholytics resemble nicotine-like compounds, whose activity in many cases is due to the presence of ammonium nitrogen [3, 9]. This resemblance between sympatholytics and nicotine-like preparations is confirmed by the fact that during the action of preparations of one group effects are observed characteristic of the other. For example, in the initial stage of action of xylocholine and bretylium, excitation of autonomic ganglia and of the adrenal medulla is observed [7, 18, 19, 25], whereas cholinomimetic compounds exhibit distinct sympatholytic properties [6, 14, 26].

Since the "ammonium end" of many nicotine-like and sympatholytic compounds is formed by two or three methyl groups, we decided to investigate the action of the simplest nicotine-like compound, tetramethylammonium iodide (TMA), and of its tertiary analog, trimethylamine hydrochloride (TRIMA), on postganglionic sympathetic nerve fibers.

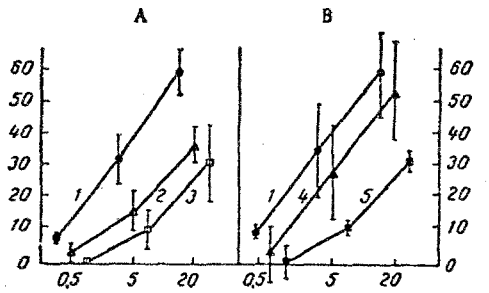

Fig. 1. Sympatholytic action of TMA (A) and TRIMA (B). Ordinate: contractions (in mm) of nictitating membrane of cat caused by stimulation of postganglionic sympathetic nerve; abscissa: frequency of electrical stimulation (pulses/sec). At each point the results of five experiments are shown with their confidence limits (P = 0.05). 1) Control experiments; 2) TMA in dose of 0.05 mmole/kg; 3) TMA in dose of 0.25 mmole/kg; 4) TRIMA in dose of 0.5 mmole/kg; 5) TRIMA in dose of 2.5 mmoles/kg.

EXPERIMENTAL METHOD

Experiments were carried out on 30 cats anesthetized with hexobarbital (100 mg/kg intraperitoneally). Using a frontally-writing isotonic lever (1:10) recordings were of contractions of the nictitating membrane caused by stimulation of the postganglionic cervical sympathetic nerve (frequency 0.5, 5, and 20/sec, duration 1 msec, amplitude 20 V, for a period of 5 sec) and by intravenous injection of L-adrenalin bitartrate in a dose of 5 μg.

Because of the inhibitory action of large doses of TMA on the respiratory center [2], all the experiments were carried out with the aid of artificial respiration.

The sympatholytic effect of the preparations was tested immediately and 30, 80, and 160 min after administration. The compounds were injected into the femoral vein in doses of 0.5 and 2.5 mmoles/kg (TRIMA) and 0.05 and 0.25 mmole/kg (TMA). The action of each dose was tested on five animals. In one series of experiments TMA was injected into adrenalectomized animals and in another series

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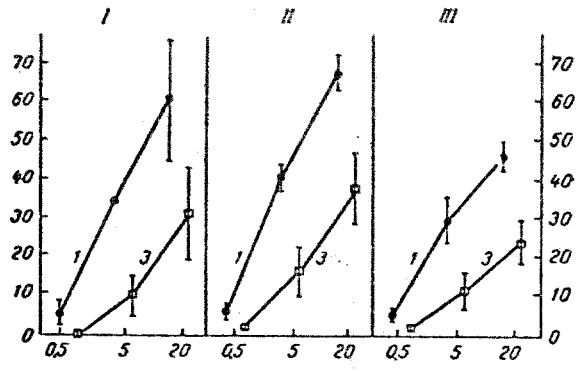

Fig. 2. Action of TMA in dose of 0.25 mmole/kg on contractions of nictitating membrane caused by stimulation of postganglionic sympathetic nerve in intact (I), atropinized (II), and adrenalectomized (III) animals. Legend as in Fig. 1.

into atropinized animals. The animals received atropine intravenously in a dose of 1 mg/kg 1 h before the experimental began.

EXPERIMENTAL RESULTS AND DISCUSSION

The results given in Fig. 1 show that TMA, in a dose of 0.05 mmole/kg, depressed the response of the nictitating membrane to stimulation of the postganglionic cervical sympathetic nerve. This effect was clearer with low frequencies of stimulation. In a dose of 0.25 mmole/kg the compound exhibited strong blocking activity, also more marked at low frequencies of stimulation. The inhibitory action of TMA was fairly stable: 2.5 h after its administration complete recovery of the original amplitude of contraction of the nictitating membrane was not observed in any experiments.

In experiments on intact, atropinized, and adrenalectomized cats TMA showed almost identical blocking activity (Fig. 2). In all these variants of the experiments the compound depressed the response of the nictitating membrane mainly to low frequencies of stimulation; the curves reflecting the response of the nictitating membrane to stimulation of the nerve at high frequencies are parallel. In no series of experiments did TMA produce a statistically significant decrease in the response of the nictitating membrane to injection of adrenalin.

TRIMA in a dose of 0.5 mmole/kg did not give statistically significant changes in the response of the nictitating membrane (Fig. 1). In a dose of 2.5 mmoles/kg, the compound significantly reduced the contractions of the nictitating membrane produced by stimulation of the sympathetic nerve but had no significant effect on contractions caused by adrenalin.

Comparison of the curves given in Fig. 1 show that TMA in a dose of 0.25 mmole/kg and TRIMA in a dose of 2.5 mmole/kg have almost identical blocking activity.

These results suggest that inhibition of contractions of the nictitating membrane caused by stimulation of the postganglionic sympathetic nerve is due to the sympatholytic activity of TMA and TRIMA. The basis for this assertion is the fact that this particular effect was not accompanied in any series of experiments by a statistically significant decrease in the response of the membrane to L-adrenalin.

Since the postganglionic cervical sympathetic nerve contains cholinergic fibers [5, 11, 21], and cholinergic biochemical systems are present in the nictitating membrane [22-24], it could be postulated that the inhibition of the response of the nictitating membrane is due to some degree to the cholinolytic action of large doses of TMA. However, after the preliminary injection of atropine, TMA was found to produce almost the same decrease in contraction of the nictitating membrane as was observed in unatropinized animals.

It was also shown that the blocking activity of TMA on adrenalectomized animals is no less marked than on intact animals. Hence, liberation of catecholamines from the adrenal medulla [9, 10] and their subsequent assimilation [12, 17, 27] have no significant role in the development of the sympatholytic action of TMA.

According to data in the literature, sympatholytics differ considerably in the character of their action [4, 20]. One distinguishing feature is that bretylium exhibits maximal sympatholytic activity at high frequencies (20-25/sec) of stimulation, whereas octatensin and reserpine exhibit their maximal sympatholytic activity at low frequencies (0.01-1/sec) [7, 8]. This feature of the action of octatensin and reserpine is associated with their action in using up the catecholamines reserves [8]. This hypothesis can also be applied to TMA and TRIMA, whose sympatholytic action is also exhibited more strongly at low frequencies of stimulation.

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