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THE BLOCKING EFFECT OF BIS-TRIETHYL-AMMONIUM SALTS ON TRANSMISSION IN THE PERFUSED SUPERIOR CERVICAL GANGLION OF THE CAT

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The action of the tetra-ethylammonium ion on the circulatory system was described by Burn and Dale (1914) as a paralysing action on sympathetic ganglia resembling that of nicotine; the same type of action was observed in a series of triethylalkylammonium salts by Hunt (1925–6). The action of tetra-ethyl-ammonium bromide on the circulatory system as well as on the sympathetic ganglion has recently been analysed by Acheson *et al.* (1946). They concluded that the predominant effect of the tetra-ethylammonium ion was a block of transmission across autonomic ganglia and that this was sufficient to explain the vaso-depressor effect. Dr. H. R. Ing suggested to us that it might be worth investigating the effect on ganglionic transmission of bis-triethylammonium salts of the general formula $[Et_3N(CH_2)_nNEt_3]X_2$, where X is the anion; such salts might be expected to have a blocking action on transmission in virtue of the triethylammonium groups and their potency might be expected to vary with the length of the polymethylene chain. Four bis-triethylammonium salts have been examined: ethylene bis-triethylammonium bromide (BTE2), prepared by Dr. H. R. Ing; and the trimethylene-, pentamethylene-, and decamethylene-bis-triethylammonium bromides, denoted by BTE3, BTE5, and BTE10 respectively, which were prepared by Mr. R. B. Barlow.

METHOD

Cats were anaesthetized with pentobarbitone and the superior cervical ganglion was prepared by Kibjakow's method (1933) modified by Feldberg and Gaddum (1934). Warm oxygenated Locke's solution was perfused through a cannula in the carotid artery at a pressure of about 120 mm. of mercury and the venous outflow from the ganglion was collected. The pre-ganglionic fibres to the superior cervical ganglion were stimulated maximally at a rate of 8 stimuli per second, for a period of 15 sec. An interval of 3 min. was allowed between each stimulation. The contraction of the nictitating membrane was

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recorded on a smoked drum by an isotonic lever. The activity of the four bis-triethylammonium compounds was compared with that of tetra-ethylammonium bromide (TE). Each drug was given in 0.1–0.2 ml. Locke's solution and was injected into the arterial cannula 1 min. before the stimulation. A cumulative effect by the drug is very liable to occur when the perfusion rate becomes slow; it was therefore decided to test the drugs in one order and then in the reverse order.

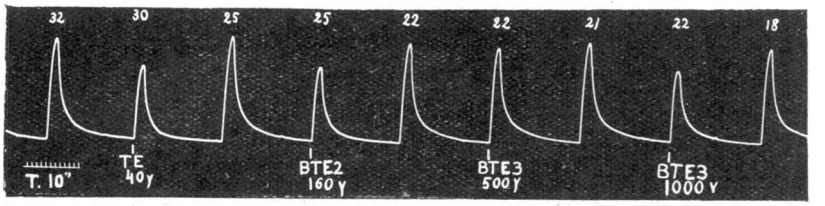

FIG. 1.—Comparison of blocking effect of tetra-ethylammonium bromide (TE) and of two bis-triethylammonium bromides (BTE2 and BTE3) on transmission in sympathetic ganglia. Perfused superior cervical ganglion of the cat. Record of the contractions of the nictitating membrane to maximal preganglionic stimulation. Rate of stimulation 8 per sec. for 15 sec. every minute. Figures above each contraction = outflow in drops per minute.

RESULTS

Fig. 1 shows the effect of BTE2 and BTE3 in comparison with that of TE on the response to preganglionic stimulation in the same preparation. The figures above each contraction of the nictitating membrane represent the venous outflow in drops per minute.

It was found that the blocking effect of the five compounds examined was in the order:

$$\underset{(200)}{\text{BTE10}} > \underset{(100)}{\text{TE}} > \underset{(33)}{\text{BTE2}} > \underset{(5)}{\text{BTE5}} > \underset{(4)}{\text{BTE3}}$$

The relative potency of these five compounds (according to their weight) has been determined on seven preparations, and, giving TE a value of 100, the mean

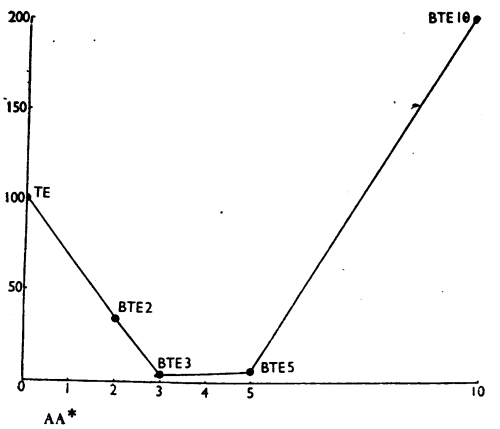

FIG. 2.—The relationship between the activity of tetra-ethylammonium bromide (TE), given a value of 100, and of bis-triethylammonium bromides (BTE2, BTE3, BTE5, and BTE10) in the perfused sympathetic ganglion of the cat. Ordinate: percentage potency. Abscissae: Number of carbon atoms in the polymethylene chain of the molecule.

figures are expressed in brackets. No excitatory action on the ganglion was observed with TE, nor with the four bis-triethylammonium compounds.

Fig. 2 shows the relationship between the activity of these compounds and the number of carbon atoms in the polymethylene chain of the molecule.

Discussion

In their two successive papers, Acheson *et al.* (1946) concluded that the tetra-ethylammonium ion exerts a purely blocking effect on ganglionic transmission. Unlike tubocurarine, the tetra-ethylammonium ion on injection never causes a contraction of the nictitating membrane, nor does it increase the response to electrical stimulation, as intocostrin was shown by Acheson *et al.* to do. It has only a "nicotine-like paralysing" action on the autonomic ganglion. The bis-triethylammonium compounds also showed no excitatory action. No experiments have been made in order to discover whether they have any muscarine actions. In general, the action of these compounds is very similar to that of tetra-ethylammonium salts. As shown in Fig. 2, lengthening of the carbon chain between the two onium ions leads to a decrease in activity until the three carbon chain compound (BTE3) is reached; with a further lengthening of the carbon chain there occurs an increase of the blocking effect, and the 10 carbon chain compound (BTE10) is twice as strong as TE.

Summary

Four bis-triethylammonium compounds have been tested on the perfused superior cervical ganglion of the cat. They have no stimulating action, but they paralyse ganglionic transmission. There is a relationship between the relative activity of these compounds and the number of carbon atoms in the polymethylene chain of their molecules. The decamethylene-bis-triethyl-ammonium bromide (BTE10) was found to be the most potent compound.

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