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THE EFFECT OF METHONIUM COMPOUNDS ON NICOTINE CONVULSIONS

BY

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Paton and Zaimis (1951) have shown that the pressor response to intravenously injected nicotine may be abolished by a previous injection of hexamethonium and that the principal action of this compound is in blocking autonomic ganglia.

The experiments reported here were designed to investigate the effects of methonium compounds on another action of nicotine, namely its power to provoke convulsions.

METHOD

Unanaesthetized mice were used for most of the experiments. Groups for comparison were from the same colony, were of the same sex, and were matched for weight. Nicotine was injected as a solution containing 0.033 mg. base/ml. saline into a tail vein and a comparison made between the convulsion rates in control groups and in groups previously treated with methonium compounds. The convulsant dose of nicotine varies considerably with the rate of injection and this was therefore standardized. All doses were given in 10 sec., a metronome being used to ensure a steady rate of delivery. Members of control and treated groups were injected alternately. The same technique was followed for the other convulsants used.

Nicotine convulsions develop within 5–15 sec. of starting an intravenous injection and their nature varies with the dose. A small dose causes co-ordinated running movements of the front legs only, a larger dose similar movements of the back legs also, and, if free, the animal runs swiftly in a straight line. With larger doses still it falls on its side, and the running movements may be succeeded by a tonic stage with respiratory arrest and, often, death. A convulsion was recorded only when the movements affected all four legs.

Animals receiving methonium compounds were given either the iodide or the bromide as a 0.5 mg./ml. solution intraperitoneally 20 min. before the nicotine injection.

In the experiments in which rats were used, hexamethonium iodide was injected intraperitoneally and nicotine subcutaneously.

The probability figures given in the Tables were obtained from Mainland's fourfold contingency tables (Mainland, 1948).

RESULTS

Table I records the results from two typical experiments. In the first, the same dose of nicotine was given to two groups of mice, one of which had received hexamethonium. In this group the convulsion rate was markedly lower. A similar result (Exp. 2) was obtained with rats.

TABLE I

EFFECT OF HEXAMETHONIUM ON NICOTINE CONVULSION RATE

Exp.	Hexamethonium iodide i.p. mg./kg.	Nicotine		No. of animals in group	No. of animals convulsed	P
		Dose mg./kg.	Route			
1	0 5	0.38 0.38	i.v. ,,	10 mice 10 ,,	10 2	<0.001
2	0 5	5 5	s.c. ,,	10 rats 10 ,,	7 1	<0.01

Fig. 1 was constructed from the data of an experiment in which four groups, each of 20 mice, were injected with nicotine at four different dose levels. Two groups had received 5 mg. hexamethonium iodide per kg. intraperitoneally 20 min. before

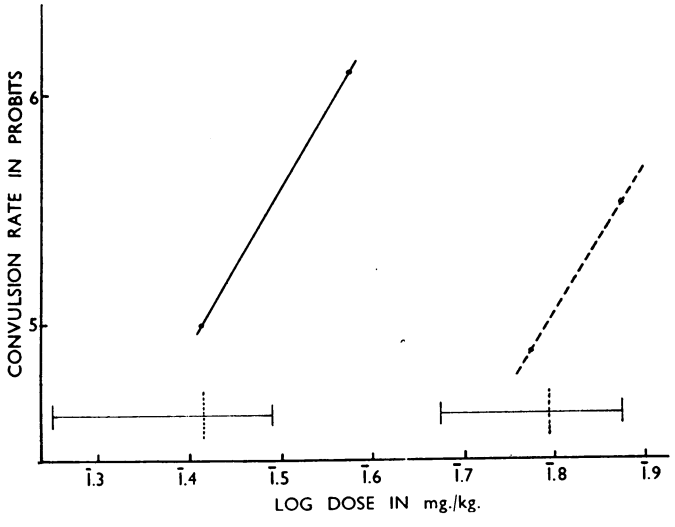

FIG. 1.—Relationship between dose and convulsion rate in two groups of 20 mice receiving intravenous nicotine only ● ——— ● and in two similar groups previously treated with hexamethonium iodide ● - - - - ●. Median convulsive dose, CD50, nicotine alone: 0.26 mg./kg. Fiducial limits [P = 0.95] 0.18–0.31 mg./kg. CD50 nicotine after C_6: 0.63 mg./kg. Fiducial limits [P = 0.95] 0.48–0.75 mg./kg.

receiving 0.25 mg. and 0.4 mg. nicotine per kg. respectively ; the two control groups received 0.6 mg. and 0.75 mg. nicotine per kg. respectively. The regression lines are parallel, and the calculated median convulsive dose of nicotine is seen to be raised from 0.26 to 0.63 mg./kg. by hexamethonium.

The effect of other members of the methonium series was then examined. Five groups of 10 mice were given tri-, tetra-, penta-, hexa- and hepta-methonium bromide respectively in a dose of 0.011 millimols per kg. (this corresponds to 5 mg. hexamethonium iodide per kg.), and a sixth group of 20 mice formed a control group. Each mouse then received 0.4 mg. nicotine per kg. intravenously. From the results (Fig. 2) it may be concluded that penta-, hexa-, and hepta-methonium bromides show a highly significant antagonism ($P<0.002$) to nicotine, whereas tri- and tetramethonium bromides have no significant action. All groups received the same dose

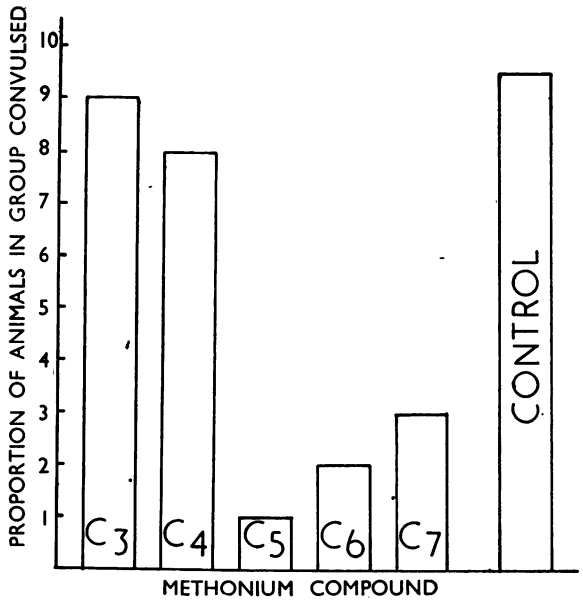

FIG. 2.—Effect of various methonium compounds (0.011 millimols/kg.) on the convulsion rate in groups of mice receiving 0.4 mg. nicotine per kg. Control group: 20 mice. Methonium-treated groups: each 10 mice.

of bromide ion which therefore exerted no antagonism to nicotine, a conclusion confirmed in another experiment (Table II, Exp. 1) in which much higher doses of bromide, given as sodium bromide, failed to lower the convulsion rate significantly.

Tetraethylammonium bromide (TEAB), which resembles hexamethonium in blocking autonomic ganglia, was found not to afford any protection against nicotine convulsions when doses varying from 5 to 50 mg./kg. (the maximum tolerated dose) were tried. A result obtained with the highest dose is recorded in Table II, Exp. 2.

TABLE II

EFFECT OF TETRAETHYLAMMONIUM BROMIDE (TEAB) AND SODIUM BROMIDE ON NICOTINE CONVULSION RATE

Exp.	Premedication		Dose of Nicotine mg./kg.	No. of mice in group	No. of mice convulsed	P
	Drug	Dose mg./kg.				
1	—	—	0.4	10	7	0.5
	NaBr	24.5	0.4	10	6	
2	TEAB	50	0.25	10	3	>0.3
	NaBr	24.5	0.25	10	5	

After the above work had been completed Bovet and Longo (1951) published a paper in which they showed that in rabbits the tremor caused by subconvulsive doses of nicotine was not inhibited by pentamethonium. We have confirmed their results and have found that the nicotine convulsions in rabbits are also not antagonized.

Experiments with other convulsants.—In view of the results obtained with nicotine it would be of special interest to know if hexamethonium exerted any anti-

convulsant action against acetylcholine and related drugs. With acetylcholine, carbachol, neostigmine, and di-*iso*propylfluorophosphonate fasciculation makes it difficult to assess the convulsant effect, and it was decided that reliable results could not be obtained by this method.

Table III gives the results of representative experiments with five other convulsants. In no case did hexamethonium cause a significant reduction in the convulsion rate.

TABLE III

ACTION OF HEXAMETHONIUM IODIDE ON CONVULSION RATE WITH VARIOUS CONVULSANTS

Convulsant	Exp.	Dose mg./kg.	No. of mice in each group	No. of mice convulsed		P
				without C_6	with C_6 (5 mg./kg.)	
Lobeline ..	1	12.5	10	4	2	0.3
	2	15	10	9	8	0.5
Leptazol ..	1	35	10	7	8	0.5
	2	40	10	8	9	0.5
Cocaine ..	1	10	10	3	4	0.5
	2	10	10	7	7	>0.6
Strychnine ..	1	0.44	10	3	7	0.18
	2	0.60	10	7	5	0.32
Picrotoxin ..	1	3.75	10	10	7	>0.1
	2	2.5	10	5	5	>0.6

Discussion

From the experiments described above it is evident that three of the five members of the methonium series tested protect mice and rats against nicotine convulsions. These are the three members (C_5, C_6, and C_7) which have the most marked ganglionic blocking powers (Paton and Zaimis, 1949). Decamethonium, the only other member available, could not be tested because of its peripheral action. Other convulsants tested, differing widely in nature, were not antagonized. This suggests that the action of hexamethonium is specific and is not explicable in terms of an alteration in permeability of the blood-brain barrier—an explanation which has been advanced by Aird and Strait (1944) for the anticonvulsant action of trypan red and certain other dyes. In particular it is interesting to note that no protection was afforded against lobeline, which resembles nicotine in many of its actions. The site at which hexamethonium exerts this effect must next be considered.

The mechanism by which nicotine provokes convulsions has never been finally settled. Local application to the motor cortex produces clonic convulsions (Rizzolo, 1929), but it has been suggested that convulsions caused by nicotine administered systemically might be wholly or in part due to anoxia resulting from respiratory arrest; or to stimulation of the carotid body (Lendle and Ruppert, 1942).

When nicotine is injected intravenously in the mouse, convulsions develop with great rapidity during the period of hyperventilation and before respiratory arrest

occurs. Respiratory arrest only takes place with doses considerably above the minimum convulsive dose and then follows, but never precedes, the convulsions. Anoxia is not therefore a cause of convulsions in these experiments.

It is not possible to be so certain that carotid stimulation does not play some part in the genesis of convulsions. Schmidt and Comroe (1940) state that stimulation of the carotid body may lead to generalized muscular activity and occasionally convulsive movements. Nicotine stimulates the carotid body, and von Euler, Liljestrand, and Zotterman (1941) have adduced evidence for this taking place at a ganglion in the carotid body area. That hexamethonium acts on the carotid body is suggested by the finding that it suppresses the cough provoked by intravenous injections of lobeline (Hillis and Kelly, 1951).

These considerations might suggest that hexamethonium antagonizes nicotine convulsions by an action on the carotid body, possibly by ganglionic blockade. Two pieces of evidence can be cited against this view. Lendle and Ruppert (1942), working with rats, found that elimination of the carotid sinuses, either operatively or by the administration of blocking agents, did not affect the development of nicotine or isolobinine convulsions. Further, in our experiments, very large doses of tetraethylammonium bromide, which has been shown by Moe, Capo, and Peralta (1948) to block the respiratory effects of intravenous nicotine in dogs, had no effect in antagonizing nicotine convulsions. The evidence points, therefore, to the conclusion that nicotine convulsions are caused by a central action. It cannot at once be assumed that hexamethonium also has a central action. It is possible that other peripheral actions, in particular its inhibition of adrenaline release, may play a part in determining the nicotine convulsion threshold.

Summary

1. When mice or rats are used as experimental animals, penta-, hexa-, and heptamethonium antagonize nicotine convulsions.

2. Tri- and tetra-methonium and tetraethylammonium show no such antagonism.

3. Hexamethonium does not antagonize convulsions caused by lobeline, leptazol, cocaine, strychnine, or picrotoxin.

4. The site of action of hexamethonium in antagonizing nicotine convulsions is discussed.

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