nuclei and muscles are similar in their immunologic properties, whereas differences in the antigenic properties of these receptors are revealed by investigation of the effect of specific serum on binding of MACT-^{3}H by the membrane preparations studied. The results thus confirm the view that the syndrome of myasthenia described previously [2] is connected with an autoimmune process involving NCR of the neuromuscular junction, which is similar in its properties to NCR of the caudate nuclei.

LITERATURE CITED

1. É. B. Arushanyan and V. A. Otellin, The Caudate Nucleus [in Russian], Leningrad (1976).
2. V. A. Smirnov, V. I. Ivanskii, and A. N. Panyukov, Byull. Éksp. Biol. Med., No. 12, 687 (1977).
3. I. P. Ashmarin, N. N. Vasil'ev, and V. A. Ambrosov, Rapid Methods of Statistical Analysis and Planning of Experiments [in Russian], Leningrad (1971), pp. 11-17.
4. C. G. Andrew, R. R. Almon, and S. H. Appel, J. Biol. Chem., 249, 6163 (1974).
5. R. J. Boegman, J. F. Manery, and L. Pinteric, Biochim. Biophys. Acta, 203, 506 (1970).
6. B. Bosmann, J. Biol. Chem., 247, 130 (1972).
7. A. W. Duggan, J. G. Halli, and C. J. Lee, Brain Res., 107, 166 (1976).
8. M. F. Giorguieff, M. L. Le Floc'h, N. B. Westfall, et al., Brain Res., 106, 117 (1976).
9. E. V. Grishin, A. P. Sukhikh, N. N. Lukyanchuk, et al., FEBS Lett., 36, 77 (1973).
10. E. Heilbronn, Croat. Chem. Acta, 47, 395 (1975).
11. G. P. Hess, J. E. Bulger, J.-J. L. Fu, et al., Biochem. Biophys. Res. Commun., 64, 1018 (1965).
12. E. Karlsson, Experientia, 29, 1319 (1973).
13. E. Karlsson, D. Baker, and G. Ponterus, Biochim. Biophys. Acta, 257, 235 (1972).
14. C. Mattson and E. Heilbronn, Croat. Chem. Acta, 47, 489 (1975).
15. B. J. Morley, J. B. Lorden, G. B. Brown, et al., Brain Res., 134, 161 (1977).
16. J. F. Riordan and B. L. Vallee, Methods Enzymol., 11, 565 (1967).

CENTRAL CHOLINOPOTENTIATING ACTION OF BENACTYZINE

V. N. Amatuni

UDC 615.217.34 (Amizylum)/.015.4

KEY WORDS: benactyzine; small doses; after-effect; cholinopotentiating action; arecoline.

A model of arecoline tremor and salivation has been suggested for the study of relations between the central and peripheral components of cholinolytic action [2]. This model later began to be widely used to study the mechanism of action of drugs and their mixtures [3, 9]. The comparative cholinolytic activity of various preparations is revealed as antagonism with cholinomimetics [10]. In these cases the cholinomimetic behaves as a factor causing disturbance of the system and the cholinolytic as a factor bringing it to rest. By means of this approach the cholinergic nature of brain systems can be revealed. Gromov [4] has used cholinomimetic testing after preliminary administration of benactyzine.

It is stated in the literature that cholinolytics have opposite effects on certain physiological reactions depending on their dose. Scopolamine, for example, increases aggression in rats in small doses, but in large doses inhibits it [13]. Scopolamine has a similar biphasic action on the behavior of rats in an "open field" [14].

In the present investigation the central action of benactyzine was investigated on a model of arecoline tremor over a wide range of doses and time intervals.

Leningrad. (presented by Academician of the Academy of Medical Sciences of the USSR S. N. Golikov.)

Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 89, No. 5, pp. 576-577, May, 1980. Original article submitted July 2, 1979.

0007-4888/80/8905-0631$07.50

TABLE 1. ED_{50} of Arecoline 30 min after Administration of Benactyzine (M± m)

Control		Experiment			
number of animals	ED_{50} of arecoline, mg/kg	dose of benactyzine, mg/kg	number of animals	ED_{50} of arecoline, mg/kg	change, % of control
12	0,20±0,06	0,1	24	0,25±0,09	123
24	0,28±0,06	0,2	36	0,11±0,06	41*
18	0,14±0,02	1,0	24	1,16±0,50	800*
24	0,16±0,04	4,0	24	1,69±0,70	1 056*
24	0,16±0,04	8,0	24	2,05±0,70	1 281*
24	0,16±0,04	20,0	24	7,47±2,60	4 669*
12	0,14±0,04	40,0	24	69,6±8,0	49 362*

*Here and in Table 2, significance of differences between values at the $P < 0.05$ level.

TABLE 2. ED_{50} of Arecoline at Different Time Intervals after Injection of Benactyzine into Rats (M ± m)

Time after injection, h	Control		Experiment			
	number of animals	ED_{50} of arecoline, mg/kg	dose of benactyzine, mg/kg	number of animals	ED_{50} of arecoline, mg/kg	change, % of control
1/2	24	0,28±0,06	0,2	36	0,11±0,06	41*
1	12	0,09±0,06		30	0,03±0,03	35
2	12	0,20±0,06		24	0,06±0,03	30*
3	12	0,20±0,03		30	0,07±0,03	34*
5	24	0,26±0,11		24	0,29±0,09	112
1/2	18	0,14±0,02	1,0	24	1,16±0,50	800*
1	18	0,14±0,02		24	0,25±0,08	169
2	18	0,14±0,02		30	0,06±0,02	45
3	18	0,20±0,03		30	0,09±0,02	43*
5	18	0,28±0,09		24	0,24±0,07	88,4

EXPERIMENTAL METHOD

Experiments were carried out in summer on albino rats weighing 150-250 g. The animals were kept under natural conditions of lighting and were given food ad lib.

A search was made for the dose of arecoline which would induce tremor in 50% of animals. For this purpose the action of several doses of arecoline was tested and the value of ED_{50} of arecoline was deduced from the results. Observations on tremor were made visually and it was deemed to be present only when the tremor extended to the whole of the animal's body. To increase the sensitivity of the method the test animal was placed at the edge of a transparent plastic box with a wall 10 mm wide and 40 cm high. The observations lasted 15 min after injection of arecoline. Each dose of the drug was tested on at least six animals. The number of animals with complete tremor was counted in each group and the values of ED_{50} for arecoline were calculated on the 15-VSM-5 computer using an algorithm for probit analysis [11].

Arecoline was injected subcutaneously at different time intervals after benactyzine. Changes in ED_{50} of arecoline 30 min after intraperitoneal injection of benactyzine in doses of 0.1-40 mg/kg were studied. When benactyzine was given in doses of 0.2 and 1 mg/kg, changes in ED_{50} of arecoline were studied in relation to the time between 30 min and 5 h after administration. Animals of the control groups received physiological saline. In cases when several experiments were conducted on the same day, one control was set up for that day.

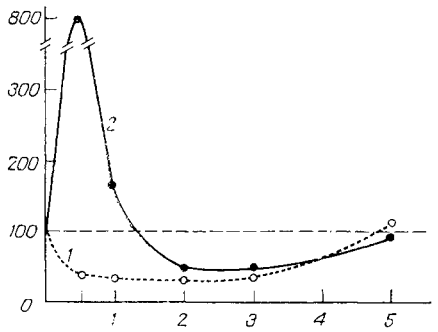

Fig. 1. Changes in ED_{50} of arecoline after preliminary injection of benactyzine in doses of 0.2 mg/kg (1) and 1 mg/kg (2). Abscissa, time after injection of benactyzine (in h); ordinate, change in ED_{50} of arecoline (in % of control, taken as 100%).

EXPERIMENTAL RESULTS

Data on changes in ED_{50} of arecoline 30 min after injection of different doses of benactyzine are shown in Table 1. The changes in ED_{50} of arecoline on different days in the control animals showed a significant difference between the extreme values ($P < 0.05$). This indicates fluctuations in the state of the cholinergic systems of the rat. Starting with a dose of 1 mg/kg the ratio between values of ED_{50} of arecoline in the experimental and control increased. The classical picture of antagonism between cholinolytic and cholinomimetic was observed.

The exception was a dose of 0.2 mg/kg of benactyzine: In this case ED_{50} of arecoline was significantly lower than its value for animals of the control group. The decrease in the dose of arecoline is evidence of increased sensitivity of the animal to the cholinomimetic. It was therefore decided to study the dynamics of changes in ED_{50} of arecoline depending on time after injection of benactyzine in doses of 0.2 and 1 mg/kg. The results (Table 2, Fig. 1) showed that under the influence of benactyzine in a dose of 0.2 mg/kg changes in ED_{50} of arecoline were in the same direction. Restoration of ED_{50} of arecoline in this case took place by the 5th hour after injection of benactyzine. When benactyzine was given in a dose of 1 mg/kg, after a sharp rise in the value of ED_{50}, a period of increased sensitivity to arecoline also was observed and was characterized by a decrease in the value of ED_{50}; this period, moreover, was longer than the period of acetylcholine receptor blockade (3.5 h compared with 1.5 h).

A similar phenomenon of hypersensitivity of pilocarpine has been observed after termination of chronic administration of scopolamine [12]. In the present case an increase in sensitivity was discovered after only a single injection of the cholinolytic. The cholinesensitizing action of cholinolytics, manifested as an increase in sensitivity to cholinomimetics, and proved in experiments on cold-blooded animals, has been demonstrated by Karasik [6, 7].

The facilitating action of small doses of a cholinolytic on certain human physiological reactions was noted by the writer previously [1] and was linked with the placebo effect of the preparations. Similar results have been obtained by other workers [5, 8], who explained them by "slight weakening of the stimulating process." The results of the present investigation show that these phenomena can be explained by the cholinopotentiating action of small doses of benactyzine. Increased sensitivity observed at the second hour of action of benactyzine in a dose of 1 mg/kg to arecoline is also evidence in support of this view. However, the compensatory effect of the internal mechanisms of adaptation of the body may be the cause of this phenomenon.

LITERATURE CITED

1. V. N. Amatuni, in: Pharmacology of Central Cholinolytics and of Other Neurotropic Agents [in Russian], Leningrad (1969), p. 46.
2. S. N. Golikov, Farmakol. i. Toksikol., No. 2, 38 (1956).

3. S. N. Golikov and S. I. Loktionov, Byull. Éksp. Biol. Med., No. 4, 61 (1966).
4. A. I. Gromov, Farmakol. Toksikol., No. 2, 145 (1975).
5. P. P. Denisenko, in: The Pharmacology of New Sedatives and Their Clinical Use [in Russian], Moscow (1962), p. 16.
6. V. M. Karasik, in: Proceedings of the 10th Congress of the All-Union Physiological Society [in Russian], Vol. 1, Moscow–Leningrad (1964), p. 63.
7. V. B. Prozorovskii, Farmakol. i. Toksikol., No. 4, 494 (1974).
8. A. T. Selivanova, The Action of Cholinergic Drugs on Higher Nervous Activity [in Russian], Leningrad (1969).
9. R. W. Brimblecome, D. M. Green, T. D. Inch, et al., J. Pharm. Pharmacol., 23, 745 (1971).
10. T. D. Inch, D. M. Green, and P. B. Thompson, J. Pharm. Pharmacol., 25, 359 (1973).
11. D. J. Finney, Probit Analysis, London (1947).
12. M. J. Friedman, J. H. Jaffe, and S. K. Sharpless, J. Pharmacol. Exp. Ther., 167, 45 (1969).
13. A. C. Karczmar and C. L. Scudder, in: Aggressive Behavior, S. Garattini and E. B. Sigg, eds., Amsterdam (1969), p. 209.
14. W. J. Stewart and S. Blain, Psychopharmacologia, 14, 291 (1975).

STIMULUS-DEPENDENT BLOCKING OF SODIUM CHANNELS IN THE RANVIER NODE MEMBRANE BY THE QUATERNARY ANTIARRHYTHMIC DRUG N-PROPYLAIMALIN (NEOGILURYTMAL)

L. D. Zaborovskaya and B. I. Khodorov

UDC 615.22.015.4:612.81

KEY WORDS: sodium channel; Ranvier node; antiarrhythmic drugs; neogilurytmal.

It was shown previously that the blocking action of local anesthetics (tertiary and quaternary amines) on sodium channels in the membrane of nerve [6, 8, 10, 14] and muscle [12] fibers may be reversibly potentiated by application of a series of depolarizing stimuli to the membrane. It was suggested that this stimulus-dependent block of the sodium channels plays an important role in the mechanism not only of the local anesthetic, but also of the antiarrhythmic action of these preparations.

Accordingly, in the investigation described below a study was made of the action of a derivative of aimalin, namely neogilurytmal (NG), one of the most effective antiarrythmic agents for use in medical practice [5, 13], on sodium channels.

EXPERIMENTAL METHOD

Experiments were carried out on the Ranvier node of isolated nerve fibers of the frog *Rana ridibunda* by the voltage-clamp method [7]. The ends of the fiber were cut on either side of the test node in isotonic CsCl solution. Cs^+ ions, diffusing along the axoplasm into the region of the Ranvier node, completely blocked the outward potassium currents. The experiments were carried out under conditions of continuous perfusion of the test node with control Ringer's solution of the following composition (in mM): NaCl 112, KCl 2.5, $NaHCO_3$ 2, $CaCl_2$ 2; pH 7.2, or with the same solution containing NG. The temperature varied in the different experiments from 12 to 15°C.

EXPERIMENTAL RESULTS

NG has no action on resting (closed) sodium channels. This is shown by the fact that exposure of the node for 5-10 min in Ringer's solution containing NG caused no appreciable decrease in the peaks of the inward sodium current (I_{Na}) in any of the experiments (n = 11),

A. V. Vishnevskii Institute of Surgery, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR S. S. Debov.)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 89, No. 5, pp. 578-580, May, 1980. Original article submitted August 1, 1979.

 0007-4888/80/8905-0634$07.50