Effect of Aceclidine on Scopolamine- and Electroshock-Induced Amnesia in Rats

M. D. Mashkovskii, V. A. Parshin, and R. B. Parimbetova

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 123, No. 3, pp. 296-298, March, 1997
Original article submitted December 22, 1995

It is found that the cholinomimetic aceclidine stimulates learning and memory processes and exerts antiamnestic effect in rats with conditioned avoidance reaction. The effect of aceclidine is not inferior to that of amiridin and surpasses that of physostigmine.

Key Words: *aceclidine, conditioned avoidance reaction; amnesia*

The first reports that the disturbances in central cholinergic processes are associated with the pathogenesis of Alzheimer disease (AD) appeared in 1976 [10,14]. The effects of different cholinergic drugs on cognitive functions were studied to effectively combat this disease. The effect of physostigmine was extensively studied in laboratories and clinics [8,12]. It was shown that β-amyloidosis, disturbed Ca homeostasis, free radicals, and other molecular mechanisms play an important role in the pathogenesis of AD [12].

Physostigmine is little effective in AD. Nevertheless, central cholinomimetic agents still attract considerable attention as potential anti-AD agents. Tacrine [9] and amiridin [7] have been recently proposed for the treatment of AD. They stimulate both the central and peripheral cholinoreactive systems. These drugs were initially used as anticurare preparations; then their positive effect on mnestic functions was discovered [1,2,12,15].

The present study examines the effect of aceclidine, a Russian-manufactured cholinomimetic preparation [4-6], on mnestic functions. Being a cyclic analog of acetylcholine, aceclidine is a tertiary (but not quaternary) base that readily crosses the blood-brain barrier.

Laboratory of Pharmacology, Russian Chemicopharmaceutical Institute; Research Center of Drug Chemistry, Moscow

MATERIALS AND METHODS

The effect of aceclidine on scopolamine-induced amnesia was studied on albino male rats weighing 180-200 g (n=120) using a step-down passive avoidance test (PAT) [13]. The rats were trained PAT (1-mA foot shock for 3 sec) during 6 sessions in a chamber with electrode floor and an escape platform; after that the acquisition and latency of PAT were determined. Immobilization on the platform for 60 sec served as the criterion of conditioning.

PAT disturbances were induced by intraperitoneal injection of scopolamine (1 mg/kg). Aceclidine (1 and 3 mg/kg) was injected subcutaneously after scopolamine. The rats were tested 2 h later for memory retention. In the control (scopolamine-treated) and experimental (scopolamine+aceclidine) groups, the number of rats immobilized on the platform for 60 sec was determined. The data were processed statistically using χ^2 test.

In experiments with electroshock-induced amnesia, the step-through passive avoidance test was used [11]. The experiments were performed on 215 male rats in a two-compartment chamber (light and dark) with an electrode floor. The animals were trained in PAT (transition from the dark to light compartment) using electrical foot shock and tested for retention 24 h later. Amnesia (elimination of the memory trace) was induced by electroshock through auricular electrodes (50 mA, 200 pulses per second).

0007-4888/97/0003-0257$18.00

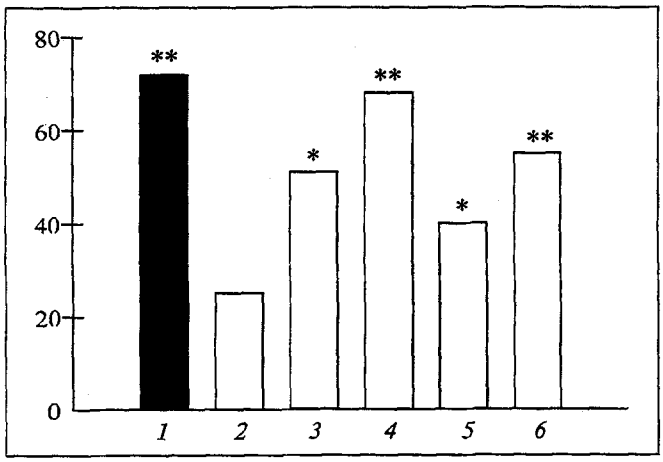

Fig. 1. Antiamnestic effect of aceclidine and physostigmine in rats under conditions of step-down passive avoidance test. Ordinate: number of animals immobilized on the platform, %. *1*) control (0.9% NaCl), trained animals after session VI; *2*) animals with amnesia (scopolamine, 1 mg/kg i.p.); *3*, *4*) aceclidine and *5*, *6*) physostigmine in doses of 1 and 3 mg/kg, subcutaneously, simultaneously with scopolamine. *$p<0.05$, **$p<0.01$ compared with scopolamine alone (control).

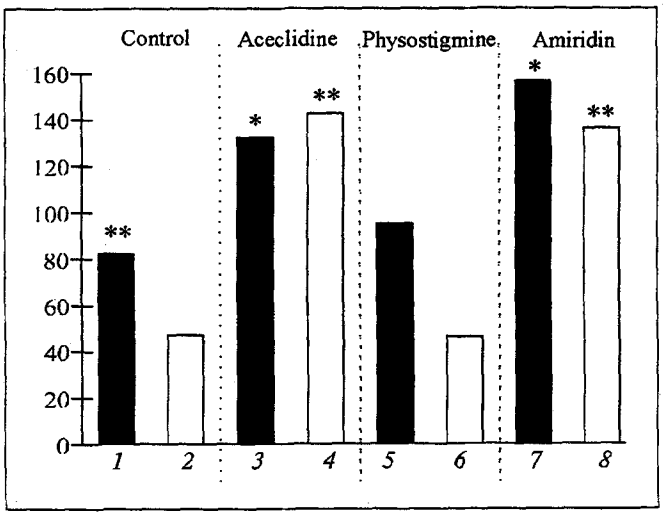

Fig. 2. Antiamnestic effect of aceclidine and physostigmine in rats under conditions of step-through passive avoidance test. Ordinate: latency of transition from the light to dark compartment, sec. *1*) control (0.9% NaCl), latency of transition to the dark compartment 24 h after training; *2*) electroshock (50 mA, 200 pulses/sec); *3*, *5*, and *7*) aceclidine, amiridin (3 mg/kg, s/c), and physostigmine (0.5 mg/kg) 24 h after training; *4*, *6*, and *8*) electroshock-induced amnesia. $p<0.05$: *compared with trained controls; **compared with amnesia.

Acquisition and antiamnestic effect of the preparations were evaluated from the step-through latency. The data were processed statistically using the Student's *t* test.

RESULTS

In the step-down experiments, the initial number of rats immobilized on the platform for 60 sec constituted 72%, while 2 h after scopolamine injection it decreased to 25%, i.e., amnesia has developed in 75% rats.

Two hours after the injection of scopolamine in combination with aceclidine in doses of 1 and 3 mg/kg, the number of rats immobilized on the platform for 60 sec constituted 50 and 68%, respectively. Thus, aceclidine in a dose of 3 mg/kg almost completely abolished the scopolamine-induced amnesia in experimental animals (Fig. 1).

In parallel experiments, in which the rats received the same doses (1 and 3 mg/kg) of physostigmine, memory trace was preserved in 40 and 55% animals, respectively.

In step-through experiments, the latency of transition into the dark compartment measured 24 h after training was 81±19 sec. Subcutaneous injection of 3 mg/kg aceclidine prolonged the latency to 132±16 sec. Physostigmine (0.5 mg/kg) slightly increased this parameter (to 94±19 sec), while amiridin (3 mg/kg, s/c) prolonged the latency to 157±24 sec (Fig. 2).

In the control group, electroshock decreased the latency to 46±16 sec. Aceclidine restored this parameter to 141±14 sec. Amiridin (3 mg/kg) produced a similar effect and even prolonged the latency to 137±20 sec. Physostigmine (0.5 mg/kg, s/c) increased the latency only to 65±24 sec (*vs.* 46±16 sec in the control).

Our experiments showed that in rats with scopolamine- and electroshock-induced amnesia aceclidine produces an antiamnestic effect somewhat surpassing that of amiridin (in experiments with electroshock-induced amnesia).

The antagonism between aceclidine and scopolamine can be attributed to the opposite effects of these drugs (cholinomimetic and cholinolytic) on the brain cholinergic systems. It is known that not only scopolamine, but also other central cholinolytics (benactyzine etc.) have a depriming effect on the central nervous system, which can be reduced by inhibitors of acetylcholinesterase and other cholinopositive drugs [3].

Similar effects of aceclidine and amiridin in electroshock-induced amnesia suggest that these preparations have the same effects on synaptic transmission, which is related to their analogous effect on the central cholinoreactive systems.

The observed antiamnestic effect of aceclidine prompts a search for antiamnestic agents among aceclidine analogs, quinuclidine derivatives.

REFERENCES

1. Yu. V. Burov, L. V. Kadysheva, and A. E. Voronin, *Byull. Eksp. Biol. Med.*, **113**, No. 1, 43-45 (1992).
2. Yu. V. Burov, L. V. Kadysheva, and S. A. Sukhanova, *Ibid.*, **111**, No. 6, No. 6, 612-614 (1991).
3. P. P. Denisenko, *Central Cholinolytics* [in Russian], Moscow (1965).
4. K. A. Zaitseva, *Farmakol. Toksikol.*, No. 2, 153-155 (1972).
5. K. A. Zaitseva, M. D. Mashkovskii, and L. F. Roshchina, *Ibid.*, No. 6, 686-690 (1964).

6. M. D. Mashkovskii and K. A. Zaitseva, *Ibid.*, No. 5, 398-406 (1960).
7. E. N. Ponomareva and T. V. Sitnik, in: *New Drugs*, No. 2, 11-14 (1990).
8. R. Cacabelos (Ed.), *Alzheimer Disease*, Barcelona (1991).
9. Z. Khachaturian and I. P. Blass (Eds.), *Alzheimer's Disease. New Treatment Strategies*, New York (1992).
10. D. M. Boven, C. B. Smith, P. White, *et al.*, *Brain*, **99**, 459-496 (1976).
11. J. Bures and O. Buresova, *Comp. Physiol. Psychol.*, **56**, 268-272 (1963).
12. R. Cacabelos, A. Nordberg, J. Camano, *et al.*, *Drugs Today*, **30**, 230-303 (1994).
13. R. Cumin, E. F. Bandle, E. Gamzu, *et al.*, *Psychopharmacology (Berlin)*, **78**, 104-111 (1982).
14. P. Davies and A. J. F. Maloney, *Lancet*, 1403-1406 (1976).
15. W. K. Summers, L. V. Majovcki, G. M. Marsh, *et al.*, *N. Engl. J. Med.*, **315**, 1241-1245 (1986).

Effect of Intravenous Infusion of Polyosm on Diuresis and Parameters of Systemic and Cerebral Hemodynamics

M. B. Plotnikov, V. I. Smol'yakova, and G. A. Chernysheva

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 123, No. 3, pp. 299-301, March, 1997
Original article submitted March 4, 1996

The effect of 30-min infusion of Polyosm (a polyethylene oxide 400 solution) is studied on anesthetized cats. The preparation stimulates diuresis and has no effect on arterial and venous pressure and cardiac and stroke indices. By the 30th min of infusion, the total peripheral and cerebral vascular resistance significantly decrease, while cerebral blood flow increases.

Key Words: *polyethylene oxide; systemic and cerebral hemodynamics; diuresis*

Intravenous administration of osmotically active diuretics modifies the hemodynamics parameters associated with distribution of intra- and extracellular fluids [2]. Polyosm, a preparation for intravenous infusions, was developed on the basis of the osmotically active compound polyethylene oxide 400. This preparation produces a rapid and stable antiedematous effect on brain tissue in models of acute ischemia and hypertonic encephalopathy.

In the present study we examined the effects of intravenous infusion of Polyosm on the major hemodynamic parameters in intact anesthetized cats.

MATERIALS AND METHODS

Experiments were performed on 14 cats of both sexes weighing 2.5-4 kg. The animals were anesthetized with sodium pentobarbital (40 mg/kg intravenously). After intravenous administration of heparin (500 units/kg), catheters were implanted in the left femoral artery for measuring systemic arterial pressure (SAP), in the left femoral vein for infusion of Polyosm, in the caudal vena cava (via the right femoral vein to the heart level) for measuring central venous pressure (CVP), and in the right heart (via the right external jugular vein) for infusion of normal saline. The branches of the right external carotid artery were ligated up to the maxillary internal artery, and a sensor of an MFV-1100 flowmeter (Nihon Kohden) was placed in it to measure cerebral blood flow. A catheter with a thermistor was inserted into the aorta via the carotid artery to record the thermodilution curve upon determination of minute volume. The volume of circulating blood was measured using the evans blue method [3]. Total peripheral vascular resistance (TPVR), cardiac and stroke indices, and cerebral vascular resistance were calculated using conventional formulas [7].

Institute of Pharmacology, Tomsk Research Center, Siberian Division of the Russian Academy of Medical Sciences

0007-4888/97/0003-0259$18.00