PHARMACOLOGICAL CORRECTION OF KETAMINE-IMPAIRED SPATIAL MEMORY OF RATS

G. V. Kovalev, V. A. Sazhin, and I. P. Kuleshova

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The dissociative general anesthetic ketamine, widely used in anesthesiologic practice, induces memory disturbance in man [4]. The pharmacological correction of ketamine-induced anmesia is an urgent problem, and it necessitates a search for an adequate model with which to study the effect of ketamine on memory processes. We know that ketamine induces retrograde amnesia of the conditioned passive avoidance reflex in rats [1], but the mnemotropic effect of ketamine is difficult to distinquish because of its analgesic and anxiolytic action [2, 3].

The aim of the present investigation was to study the effect of ketamine on performance by rats of a conditioned reflex of obtaining food reinforcement in a radial maze, and the possibility of pharmacological correction of ketamine-impaired spatial memory.

EXPERIMENTAL METHOD

Experiments were carried out on 32 noninbred male albino rats weighing 180-260 g.

A wooden radial maze consisted of a central platform (diameter 25 cm) with eight radial corridors (length 42 cm, width 9 cm, height of the plexiglass sides 5.5 cm), raised to a height of 70 cm above the floor [8]. At the end of each corridor, a piece of cheese weighing 100 mg, serving as food reinforcent, was placed in a metal dish. Before training in the radial maze, the animals were adapted for 3 days to the situation (for 5 min daily), after which they were subjected to food deprivation. Later, once a day, each animal was placed in the maze to obtain food, and removed after it had visited all eight corridors, or after 5 min. The rats' short-term memory was studied by the delayed choice reaction, when after a 4th visit to the corridor, the animal was placed for 5 min in a dark chamber, then returned to the maze and allowed to obtain the remaining reinforcement.

Ketamine ("Calipsol"), physostigmine salicylate, aspartic acid, and haloperidol were of Hungarian origin, and injected intraperitoneally into the animals in 0.14 M NaCl in a volume of 0.2 ml. The numerical results were subjected to statistical analysis by the nonparametric Wilcoxon–Mann–Whitney test.

EXPERIMENTAL RESULTS

During the experiments in the radial maze, the state of the animals' spatial memory was assessed by the number of incorrect visits to the corridors and the time taken to obtain reinforcement in eight of the radial corridors. Training of the rats in the radial maze continued for 10 days until the animals had reached a performance rate of 1.3 ± 0.5 mistaken visits to obtain food. The rats were then divided into two groups: those with a spatial (SS) and a nonspatial (NSS) strategy, depending on preference by the animals of a way through the maze [6, 11].

When ketamine was injected 15 min before testing in a dose of 10 mg/kg, but not of 1 and 5 mg/kg, it impaired the solution to the problem of seeking food in the radial maze in rats with SS. The number of mistakes in this case increased from 2.0 ± 0.7 to 8.7 ± 3.6 ($p < 0.05$) and the time of passage through the maze increased from 87.7 ± 18.6 to 160.4 ± 31.7 sec ($p < 0.05$, Fig. 1). The accuracy of choice in animals with NSS was unchanged by ketamine in the above-mentioned doses. Ketamine

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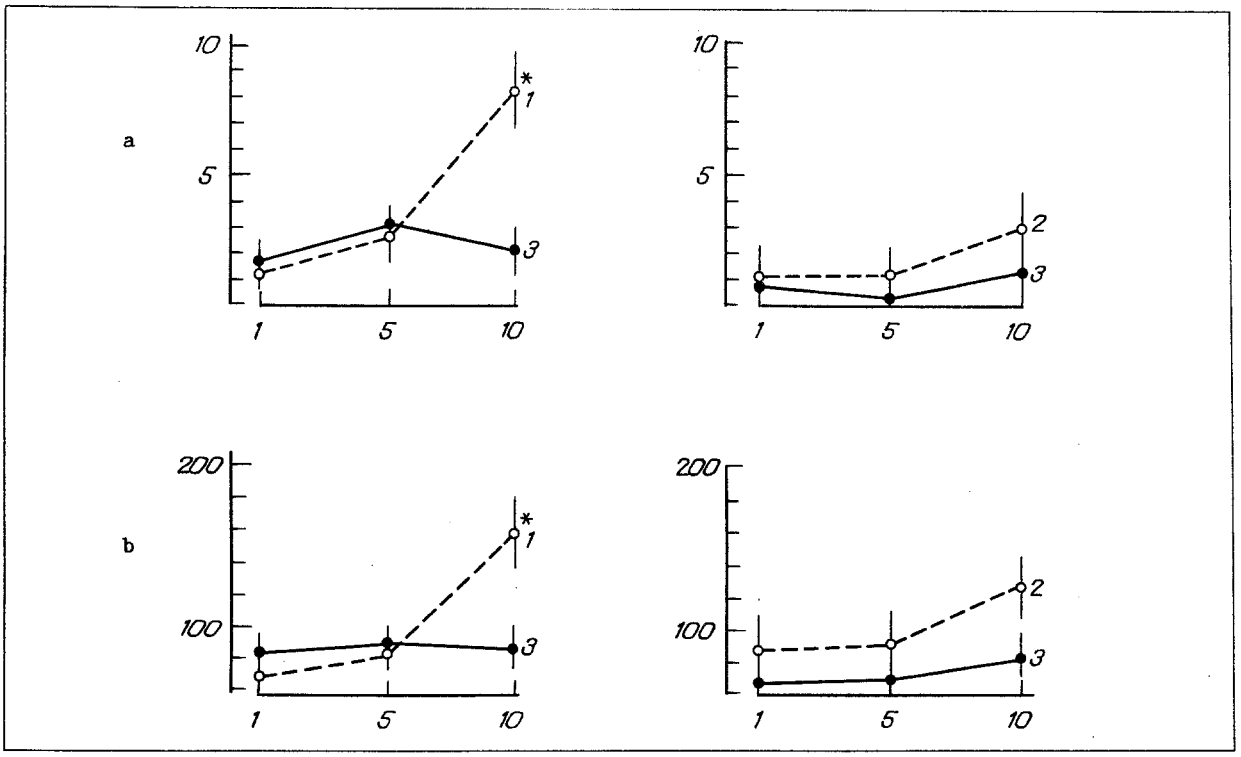

Fig. 1. Effect of ketamine on performance of conditioned reflex of obtaining food reinforcement by rats with SS (1) and NSS (2) by a strategy in an eight-passage radial maze. Control group received physiological saline. Abscissa, dose of ketamine (in mg/kg); ordinate: a) number of incorrect visits; b) time required for taking reinforcement from eight corridors (in sec), *$p < 0.05$ Compared with control.

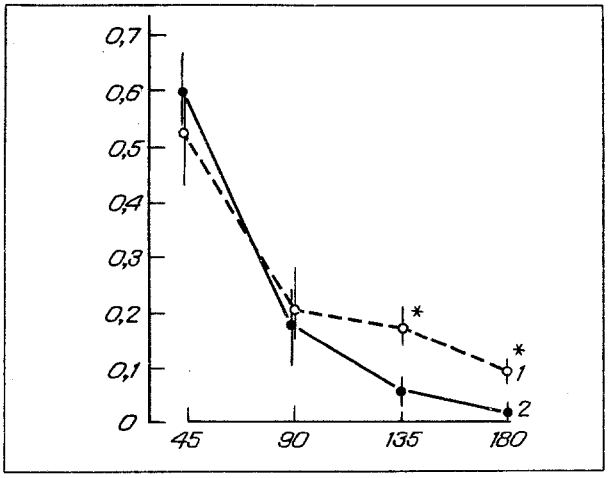

Fig. 2. Effect of ketamine (10 mg/kg) (1) on investigative behavior of rats in eight-passage radial maze. Control group (2) received physiological saline. Abscissa, angle of turning when making choice (in degrees); ordinate, probability of choosing corridor at the given angle. *$p < 0.05$ Compared with control.

in a dose of 10 mg/kg caused the appearance of a specific pattern of investigative behavior of the rats and a change of their habitual ways in the maze. In the control, rats with SS and NSS, while visiting mainly the corridors arranged at an angle of 45 and 90°, virtually never visited those lying an an angle of 135 and 180° from the current point of choice. Under the influence of

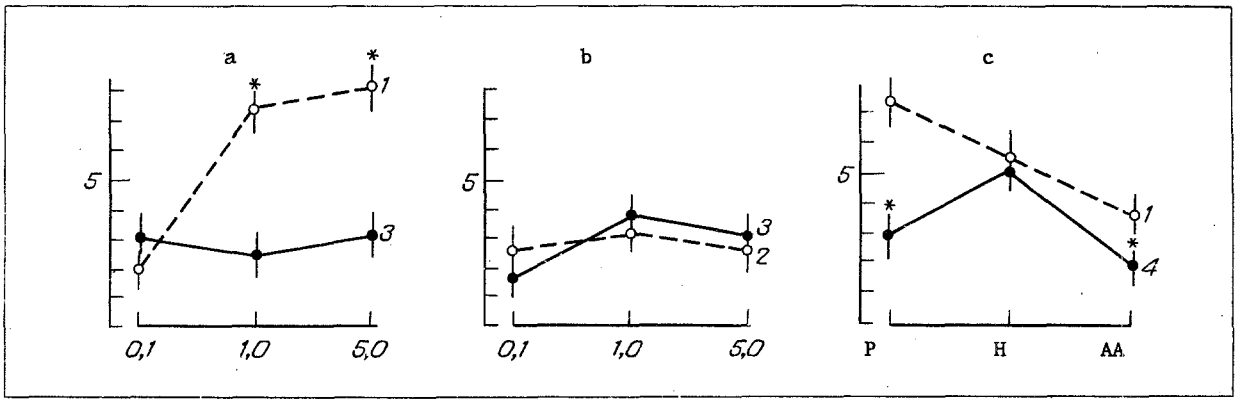

Fig. 3. Effect of ketamine on performance of delayed choice reaction by rats with SS (1) and NSS (2) by a strategy in an eight-passage radial maze. Control group (3) received physiological saline. Abscissa: a, b) dose of ketamine (in mg/kg), c) injection of ketarnine (5 mg/kg) and physostigmine (0.1 mg/kg, P), ketamine (5 mg/kg), and haloperidol (0.1 mg/kg, H), and ketamine (5 mg/kg) and aspartic acid (500 mg/kg, AA) (4). Ordinate: a, b, c) number of mistaken visits. *$p < 0.05$ Compared with control (a, b) and compared with (1) (c).

the drug the number of uncharacteristic visits to corridors at an angle of 135 and 180° rose sharply, as also did the number of repeat visits to the same corridors (Fig. 2).

In the delayed choice reaction ketamine, if injected 15 min before the test began in doses of 1 and 5 mg/kg, increased the number of incorrect visits to 7.2 ± 1,2 and 7.4 ± 2.5 respectively compared with 2.8 ± 1.5 and 3.3 ± 1.6 in the control ($p <$ 0.05) in rats with SS but did notaffect the performance of delayed choice in rats with NSS (Fig. 3). The acetylcholinesterase inhibitor physostigmine, in a dose of 0.1 mg/kg, reduced the number of mistakes made by animals after injection of ketamine, but in a dose of 0.5 mg/kg it potentiated ketamine-induced ataxia, and this greatly impaired the search for reinforcement in the maze. The dopamine receptor antagonist haloperidol, in a dose of 0.1 mg/kg, did not abolish ketamine amnesia, but in a dose of 0.5 mg/kg it had a marked sedative effect and suppressed the search for food. A significant decrease in the number of incorrect visits to the corridors was observed if aspartic acid was injected in a dose of 500 mg/kg (Fig. 3) 1 h before injection of ketamine.

Thus ketamine, in a dose of 10 mg/kg, impaired performance of the habitual search for food in a radial maze by rats with SS, but in doses of 1 and 5 mg/kg it disturbed the animals' short-term (working) spatial memory. This suggests that ketamine may disturb activity of neurons in the septohippocampal region of the brain, which play a key role in the formation of spatial memory in rodents [6]. The results relating to correction of ketamine amnesia by physostigmine and aspartic acid are evidence of interaction of ketamine with cholinergic and glutamate/aspartatergic, systems of the hippocampus, which are involved in spatial information processing [6, 9].

Being a phencyclidine analog, ketamine gives rise to varied psychotropic effects due to stimulation of phencyclidine/sigma-opiate receptors, coupled with N-methyl-D-aspartate (NMDA)-receptors of excitatory amino acids [5]. It can be tentatively, suggested that the disturbance of spatial memory by ketamine also is based on blockade of NMDA-receptors, which are located together with phencyclidine receptors in hypothalamic structures [7]. Ketamine amnesia in rats in a radial maze is not connected with activation of the dopaminergic system of the brain, for haloperidol, a dopamine receptor antagonist, did not restore the disturbed habit. Our own results are largely in agreement with other data [10] relating to correction of phencyclidine-induced disturbance of the conditioned avoidance reaction in mice by physostigmine, but not by haloperidol, and they suggest that a model of training rats in a radial maze can be used to study the effect of antagonists of receptors of excitatory amino acids on memory processes in animals.

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ROLE OF THE PERIPHERAL ADRENERGIC COMPONENT IN EFFECT OF ANTIDEPRESSANT ON EXPERIMENTAL BEHAVIORAL DEPRESSION IN CATS

E. B. Khaisman and V. V. Kushnarev

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Pharmacological, biochemical, and neurochemical factors of psychotropic activity of the new antidepressant befol (synthesized at the Research Institute of Pharmacology Academy of Medical Sciences of the USSR, and Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR) have been studied on models of experimental depressive states. It has been shown that its normalizing therapeutic effect is based on activation of functionally weakened adrenergic and serotoninergic structures of the central and peripheral nervous system [1-3]. Various other antidepressants and, in particular, nialamide, which possess similar mechanisms of action on neurotransmitter systems, have been used on the same model for the purpose of comparative study [5, 7, 9, 10]. The object for special study in the investigation described below was the morphological and functional state of peripheral adrenergic nerves in a reserpine model of behavioral depression in cats, and also dependence of restoration of their neurotransmitter activity on the action of befol and nialamide.

EXPERIMENTAL METIIOD

Experiments were carried out on 30 noninbred male cats weighing 3.5-4.5 kg. A state of behavioral depression was induced by subcutaneous injection of reserpine in a single dose of 0.1 mg/kg [4]. Befol in a dose of 0.5 mg/kg and nialamide in a dose of 15 mg/kg were injected by the enteral route. In the case of treatment of depression, the drugs were admini stered twice a day (24-48 h after reserpine), whereas for prevention, they were given 3 h before the experiment began. The duration of the experiments varied from 24 to 144 h. At each stage of development of depression various parameters of somatic and autonomic disorders and also changes in the emotional and motivational spheres characteristic of the state of depression in the experimental animals were recorded. Material for histochemical study consisted of different parts of the serous membranes (mesentery, pericardium, and pleura). Their adrenergic innervation was demonstrated by the Falck–Hillarp fluorescence-microscopic method. For quantitative evaluation of the intensity of noradrenalin-induced luminescence, the FÉU-19 photosensitive attachment was used with the ML-2 microscope as described previously [6]. Material was taken 24, 48, 96, and 144 h after the beginning of the experiment. The animals were killed by air embolism.

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