PHARMACOLOGY AND TOXICOLOGY

Effect of Noopept and Afobazole on the Development of Neurosis of Learned Helplessness in Rats

A. A. Uyanaev, V. P. Fisenko, and N. K. Khitrov

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We studied the effects of new psychotropic preparations noopept and afobazole on acquisition of the conditioned active avoidance response and development of neurosis of learned helplessness in rats. Noopept in doses of 0.05-0.10 mg/kg accelerated acquisition of conditioned active avoidance response and reduced the incidence of learned helplessness in rats. Afobazole in a dose of 5 mg/kg produced an opposite effect, which is probably related to high selective anxiolytic activity of this preparation.

Key Words: *noopept; afobazole; neurosis; learned helplessness*

Defense conditioned behavior is a very popular model in experimental psychopharmacology [2,4]. This behavior is represented by standard reactions or modifications of defensive conditioned responses to electrical stimulation during exposure to light or sound [4]. This approach is determined by a wide knowledge about active and passive defense conditioned responses in animals. On the other hand, acquisition of the avoidance response sometimes cannot reveal nootropic and anxiolytic properties of compounds [2]. Experimental neurosis of learned helplessness (LH) developed in a new situation serves as a model for acquisition of the conditioned active avoidance response (CAAR) and allows evaluating the properties of psychotropic preparations [6,7,8-10].

The effects of new preparations noopept (nootropic drug with nootropic and anxiolytic properties) and afobazole (selective anxiolytic) [5] synthesized at the Institute of Pharmacology (Russian Academy of Medical Sciences) on the development of neurosis of LH in rats were studied on the model of acquisition of CAAR [6,7]. The nootropic preparation piracetam and anxiolytic buspiron with nootropic, anxiolytic, and other activities served as the reference preparations [1,3].

MATERIALS AND METHODS

Experiments were performed on 154 male outbred albino rats weighing 250-300 g. The animals were kept in cages (4-5 rats per cage) in a vivarium under standard conditions. The light period was 12 h. The rats were randomly divided into groups. The test preparations were injected intraperitoneally (1 ml) in 3 doses. Control animals received 0.9% physiological saline. Other rats received piracetam (100, 300, and 500 mg/kg), noopept (0.05, 0.1, and 0.5 mg/kg), buspiron (0.5, 1, and 5 mg/kg), or afobazole (1, 5, and 10 mg/kg). The drugs were administered once a day throughout the period of learning. Experiments were performed daily in the same time. The rats were trained to press a lever (instrumental defense reaction) in response to the conditioned stimulus. Continuous light served as the conditioned stimulus, while electrical current delivered through a floor grid (10-20% above pain threshold, 5 sec with 40-sec intervals) served as the unconditioned stimulus. The lever was positioned near the wall of a chamber at a distance of 2 cm from the floor. Electrical stimulation was terminated when

Department of Pharmacology, Department of General Pathology, Therapeutic Faculty, I. M. Sechenov Moscow Medical Academy. ***Address for correspondence:*** uyanaev@mmascience.ru. Uyanaev A. A.

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the animals pressed the lever over 3-sec exposure to conditioned stimuli. This process promoted further instrumental training during search activity. The rats could avoid electrical stimulation by pressing the lever during light-on. However, only 1 of 4 correct pressings was not followed by pain stimulation. The rats were subjected to 40 training sessions per day. The response was considered to be elicited when the total number of correct reactions surpassed a priori probability for their random performance (χ^2 test, p=0.05). The rate and effectiveness of learning were determined by the number of instrumental reactions, count of combinations required for elicitation of CAAR, ratio of correct reactions (in relation to the total number of reactions), and average latent period (ALP) of reactions. The incidence of LH was determined in each group of rats.

RESULTS

Control rats were characterized by moderate unlearning in the test of CAAR. The incidence of LH, ALP, and number of correct instrumental reactions (CR) in these animals were 55.6%, 3.4 sec, and 11.2%, respectively. Noopept increased locomotor, orientation, and exploratory activity of rats. In a dose of 0.1 mg/kg this drug increased the number of CR to 18.7% (*vs*. 11.2% in the control). Thus, the animals displayed a lower number of incorrect lever pressings. ALP decreased from 3.4 to 1.2 sec. Neurosis of LH developed in only 16.6% rats (*vs.* 55.6% in the control). Noopept in doses of 0.05 and 0.5 mg/kg had no effect on the number of CR. Behaviorally, the animals were more active. Noopept in a dose of 0.05 mg/kg reduced ALP to 1.9 sec; the number of CR was 45.4%. The reference preparation piracetam in a dose of 100 mg/kg produced similar effects. The number of CR was 15.4%. Piracetam decreased ALP and the incidence of LH to 1.6 sec and 28.6%, respectively. No significant changes were observed after treatment with piracetam in a dose of 300 mg/kg. The positive effect of piracetam became less pronounced after increasing its dose to 500 mg/kg. The number of CR and the incidence of LH were 8.4 and 63.6%, respectively. Probably, increasing the dose of piracetam to 500 mg/kg was accompanied by inversion of the nootropic effect into anxiolytic activity. In this dose piracetam increases pain threshold and suppresses behavioral activity directed at avoidance of electrical stimulation. Noopept also possesses nootropic and anxiolytic properties.

Afobazole suppressed locomotor and exploratory activity in rats. The drug in a dose of 5 mg/kg decreased the number of CR to 7.3%. We revealed no significant changes after administration of afobazole in doses of 1 and 10 mg/kg. Afobazole in a dose of 1 mg/kg increased ALP to 5.3 sec. After treatment with afobazole in higher doses (5 and 10 mg/kg) ALP increased insignificantly. The incidence of LH increased to 66.7% after administration of afobazole in doses of 1 and 5 mg/kg. The reference preparation buspiron in a dose of 5 mg/kg caused similar changes. However, in doses of 0.5 and 1 mg/kg this preparation produced an opposite effect. Buspiron increased the number of CR, reduced the incidence of LH, and decreased ALP. It was probably related to the nootropic effect of buspiron, which improved learning. The anxiolytic preparation afobazole does not have these properties and, probably, impairs learning in rats.

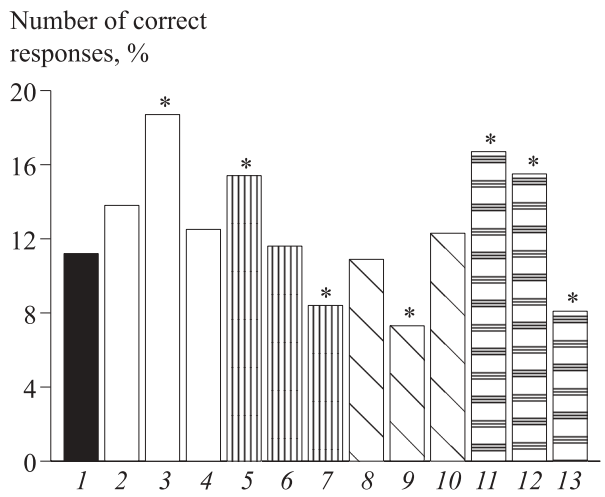

Fig. 1. Number of correct instrumental reactions after treatment with noopept (light bars), piracetam (vertical shading), afobazole (slant shading), and buspiron (horizontal shading). *p<0.05 compared to the control. Here and in Figs. 2 and 3: control (*1*); noopept in doses of 0.05 (*2*), 0.1 (*3*), and 0.5 mg/kg (*4*); piracetam in doses of 100 (*5*), 300 (*6*), and 500 mg/kg (*7*); afobazole in doses of 1 (*8*), 5 (*9*), and 10 mg/kg (*10*); and buspiron in doses of 0.5 (*11*), 1 (*12*), and 5 mg/kg (*13*).

Our results indicate that noopept in doses of 0.05 and 0.1 mg/kg accelerates learning of CAAR and re-

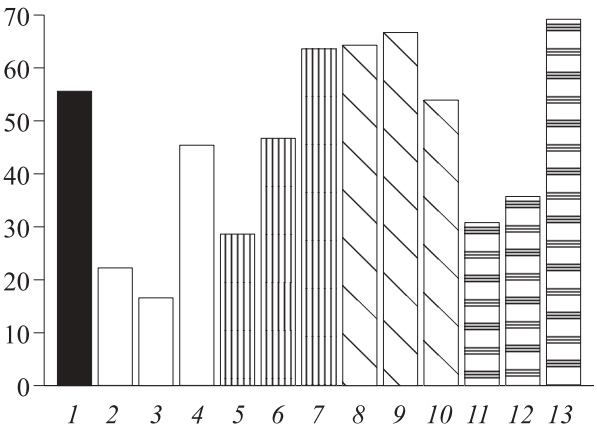

Fig. 2. Incidence of learned helplessness (LH) after administration of noopept (light bars), piracetam (vertical shading), afobazole (slant shading), and buspiron (horizontal shading). Ordinate: incidence of LH, %.

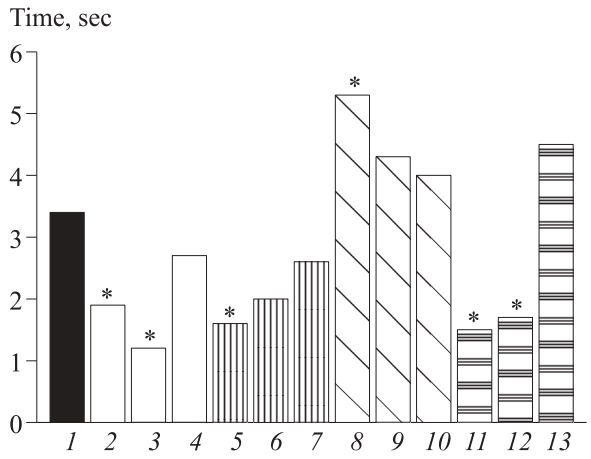

Fig. 3. Mean latent periods of instrumental reactions after treatment with noopept (light bars), piracetam (vertical shading), afobazole (slant shading), and buspiron (horizontal shading). *$p<0.05$ compared to the control.

duces the incidence of neurosis of LH in rats. Piracetam in a dose of 100 mg/kg produces similar effects. Afobazole in a dose of 5 mg/kg causes an opposite effect. The reference preparation buspiron in doses of 0.5 and 1 mg/kg accelerates acquisition of CAAR and decreases the incidence of LH. As differentiated from the anxiolytic preparation afobazole, buspiron in doses of 0.5 and 1 mg/kg possesses nootropic properties.

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