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Studies of Long-Term Noopept and Afobazol Treatment in Rats with Learned Helplessness Neurosis

A. A. Uyanaev and V. P. Fisenko

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Long-lasting effects of new Russian psychotropic drugs Noopept and Afobazol on active avoidance conditioning and formation of learned helplessness neurosis were studied on an original experimental model in rats. Noopept eliminated the manifestations of learned helplessness after long-term (21-day) treatment by increasing the percent of trained animals. Afobazol was low effective in preventing manifestations of learned helplessness, but if used for a long time, it reduced the incidence of learned helplessness development by increasing the percent of untrained animals.

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

Studies on a model of learned helplessness neurosis using the method of training in uncertain environment showed that Noopept in doses of 0.1, 0.5, and 1.0 mg/kg significantly increased the number of trained animals and prevented neurotization after training with constant (100%) and partial (25%) reinforcement of correct reactions [4,5,7]. Noopept in a dose of 0.5 mg/kg was most effective: none of the animals developed learned helplessness neurosis after training with 100% reinforcement and only 7.7% animals demonstrated signs of learned helplessness after training with 25% reinforcement.

Afobazol in doses of 1, 5, and 10 mg/kg appreciably decreased the number of trained animals and decreased the incidence of learned helplessness formation after training with constant and partial reinforcement of correct reactions. The most effective dose of afobazol was 5 mg/kg: up to 85.7% animals with signs of learned helplessness at 25% reinforcement. These effects of noopept and afobazol were observed after 3-6-day treatment with the drugs (before attaining learning criterion).

Effects of noopept and afobazol on the course of learned helplessness neurosis after multiple injections attract special interest, because these drugs are clinically prescribed for long-term treatment.

MATERIALS AND METHODS

Experiments were carried out on adult outbred albino male rats (n=376; 250-300 g) kept under vivarium conditions with 12-h light period with free access to water and standard food.

The operant training was performed in a modified setup for active avoidance conditioning under conditions of uncertain environment [4,5,7].

The animals were intraperitoneally injected (1 ml/kg) with noopept (0.1, 0.5, and 1.0 mg/kg) and piracetam (100, 300, and 500 mg/kg; reference drug), afobazol (1, 5, and 10 mg/kg), and buspiron (0.5, 1.0, and 5.0 mg/kg; reference drug) and diazepam (0.05, 0.1, and 0.5 mg/kg; reference drug). Control rats were injected with the same volume of saline. Stability of active avoidance behavior was

Department of Pharmacology, Therapeutic Faculty, I. M. Setchenov Moscow Medical Academy

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tested after 48 h and 7 days [6]. The animals with learned helplessness neurosis were injected with noopept and afobazol for 21 days [1,6], after which stability of the active avoidance behavior was repeatedly tested.

In series I of the experiments constant (100%) reinforcement of correct reactions was used: correct operant act in response to presentation of a conditioned stimulus saved the animal from electrocutaneous shock in 100% cases.

In series II of the experiments partial (25%) reinforcement was used: correct operant acts were followed by electrocutaneous shock in 1 of 4 cases at random.

The criterion of conditioning was statistically significant excess of the total number of operant acts performed in response to conditioned stimulus over the probable level of their chance performance (χ^2 test at p=0.05).

The rate of training and exploratory activity were evaluated by the number of trained and untrained animals and cases of learned helplessness in each group, total number of all combinations (conditioned and unconditioned stimuli) needed for conditioning, total number of all operant acts needed for conditioning (summary number of lever pressings per experiment), number of "correct" operant acts (performed in response to presentation of the conditioned signal) in comparison with the total number of operant acts, latency of operant acts, behavioral activity in five conditionally distinguished periods of training (mean number of instrumental reactions per cycle).

In addition, various drug administration schedules were used (directly before training, before testing the reflex stability, after training), which helped evaluate the effects of these drugs on certain memory phases during active avoidance conditioning.

Experimental data were classified and processed using selective statistical method and the method of least squares using SPSS 9.0 software. The significance of differences was evaluated by Student's t test (at p<0.05).

RESULTS

Noopept in doses of 0.1 and 0.5 mg/kg was effective in active avoidance conditioning when injected not only before training, but also before testing after 48 h. This drug (1 mg/kg) produced a similar effect in testing of reflex stability 7 days after training, and was effective in all doses. Piracetam (100, 300, and 500 mg/kg) deteriorated active avoidance performance. According to the concept attributing the drug efficiency at various routes of administration to the predominant effects on different phases of memory processing [3,6], our observations indicate that noopept facilitated the initial processing, fixation, and consolidation of information and its retrieval. Presumably, in contrast to noopept, piracetam modulates just the initial phases of information processing, without improving (or even deteriorating) the phase of memory retrieval.

In rats with signs of learned helplessness long-term treatment (for 21-day) with noopept in doses of 0.1, 0.5, and 1 mg/kg increased the number of trained animals, restored exploration activity, eliminated visual signs of neurotization, and normalized body weight and fur status. Noopept was most effective in a dose of 0.5 mg/kg: no signs of learned helplessness were detected after training with 100% reinforcement and only 7.1% animals demonstrated these signs after training with 25% reinforcement (Tables 1 and 2). The positive effects of 0.1 and 1.0 mg/kg noopept were less pronounced, but the results were better than in the control group (up to 12% cases of learned helplessness).

Hence, the results of 21-day treatment of rats with signs of learned helplessness with noopept suggest that this drug not only prevented, but also eliminated the manifestations of learned helplessness.

The use of anxiolytics under similar conditions was based on the assumption that at the level of probability of chance performance of correct instrumental reactions (0.05) and probability of reinforcement of correct responses (25%) least favorable for training, the decrease in the levels of anxiety and fear would maximally reduce the information significance of exploratory reactions.

Analysis of parameters of behavioral activity in testing of active avoidance stability showed that afobazol injected not only before training but also before subsequent testing after 48 and 7 days exhibited similar efficiency. The reference drugs (buspiron and diazepam) were less effective in this test 7 days after the end of treatment at all studied doses.

In rats with manifestations of learned helplessness long-term treatment with afobazol (1, 5, and 10 mg/kg) appreciably decreased the percentage of trained animals (to 18%), significantly increased the number of combinations in exploratory activity adequate to the controls. However, the percentage of animals with signs of learned helplessness (Tables 1, 2) did not surpass 45% for the most unfavorable conditions of training (up to 64.7% in the control).

Afobazol did not prevent the formation of learned helplessness, but the results of long-term (21-day) treatment of neurotic rats with this drug indi-

TABLE 1. Changes in the Percentage of Trained, Untrained, and Neurotized Animals under the Effect of Noopept and Afobazol Trained with Constant (100%) Reinforcement

Parameter	Control	Noopept, mg/kg			Afobazol, mg/kg		
		0.1	0.5	1.0	1.0	5.0	10.0
Trained animals	36.4	92.3	100	92.9	33.3	27.3	25
Untrained animals	18.2	7.7		7.1	41.7	63.6	50
Cases of learned helplessness neurosis	45.5	—	—	—	25	9.1	25

TABLE 2. Changes in the Percentage of Trained, Untrained, and Neurotized Animals under the Effect of Noopept and Afobazol Trained with Partial (25%) Reinforcement

Parameter	Control	Noopept, mg/kg			Afobazol, mg/kg		
		0.1	0.5	1.0	1.0	5.0	10.0
Trained animals	23.5	85.7	87.5	81.3	18.8	25	18.2
Untrained animals	11.8	12.5	7.1	6.3	43.8	41.7	36.4
Cases of learned helplessness neurosis	64.7	—	7.1	12.5	37.5	33.3	45.5

cate that it eliminated manifestations of learned helplessness. In contrast to noopept, afobazol treatment decreased the number of animals with learned helplessness by increasing in the percentage of untrained rats, but not by improving learning. Conditioning was impossible in these animals, but their exploratory activity was higher, there were no signs of neurotization, their body weight and fur status normalized.

Thus, noopept effectively eliminates the manifestations of learned helplessness neurosis after long-term treatment due to the increase in the number of trained animals. Long-term treatment with afobazol also reduced the incidence of learned helplessness in rats, but due to the increase in the number of untrained animals.

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