# Comparison of the Neurotropic and Stress-Protecting Properties of Piracetam and Pyrido[1,2-a]Pyrimidine Derivative

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A new pyrido[1,2-a]pyrimidine derivative causes psychostimulation in albino rats expressed in accelerated learning during the elaboration of the avoidance reaction in a shuttle box. It is also shown that on a model of acute emotional stress induced by a disturbance of the unambiguity of cause-effect relationships in the experimental setting this compound exhibits a stress-protecting effect which is comparable to the effect of piracetam.

**Key Words:** *stress; nootropics; antidepressants; psychostimulators; pyridopyrimidines*

As we showed previously, the new pyrido[1,2-a]pyrimidine (PP) derivatives synthesized at the Research Institute of Pharmacology, Russian Academy of Medical Sciences, offer a spectrum of useful psychotropic properties. As quaternary salts of pyridopyrimidine with relatively simple substitutes (methyls, phenyls, and oxy groups) in a basic bicyclic structure, these compounds exert marked psychostimulatory and antidepressive effects in experiments comparable in efficacy to the known antidepressants and psychostimulators with nootropic action.

The aim of the present investigation was to correlate the psychostimulatory effect of one of the promising compounds of the PP group - perchlorate-2,4-dimethylpyrido[1,2-a]pyrimidine (PION-6) with the properties of the known psychostimulator piracetam from the group of nootropics.

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## MATERIALS AND METHODS

The methods used for the study were the elaboration of the avoidance reaction (AR) and reversible functional failure of the AR, which has shown its efficacy in the study of psychopharmacological correction of behavior impaired by stress [4,5,7].

The study was carried out on male outbred rats weighing 180-220 g, divided into 3 groups. The rats of the first group ($n$=8) were injected with piracetam (300 mg/kg), animals of group 2 ($n$=6) were given physiological saline, and rats of group 3 ($n$=10) received PP derivative (20 mg/kg). The substances and physiological saline were administered intraperitoneally in a volume of 0.4-0.5 ml throughout the course of conditioning 30 min prior to each test.

In all animals the AR was learned in the course of 7 days by 25 presentations per test in a shuttle box. The conditioned stimulus was a sound (10 sec) and electric current served as the unconditioned stimulus (10 sec). The movement of the animal from one half of the box to the other half switched off both stimuli.

With AR formation completed, the malfunction of the reaction was performed as described previ-

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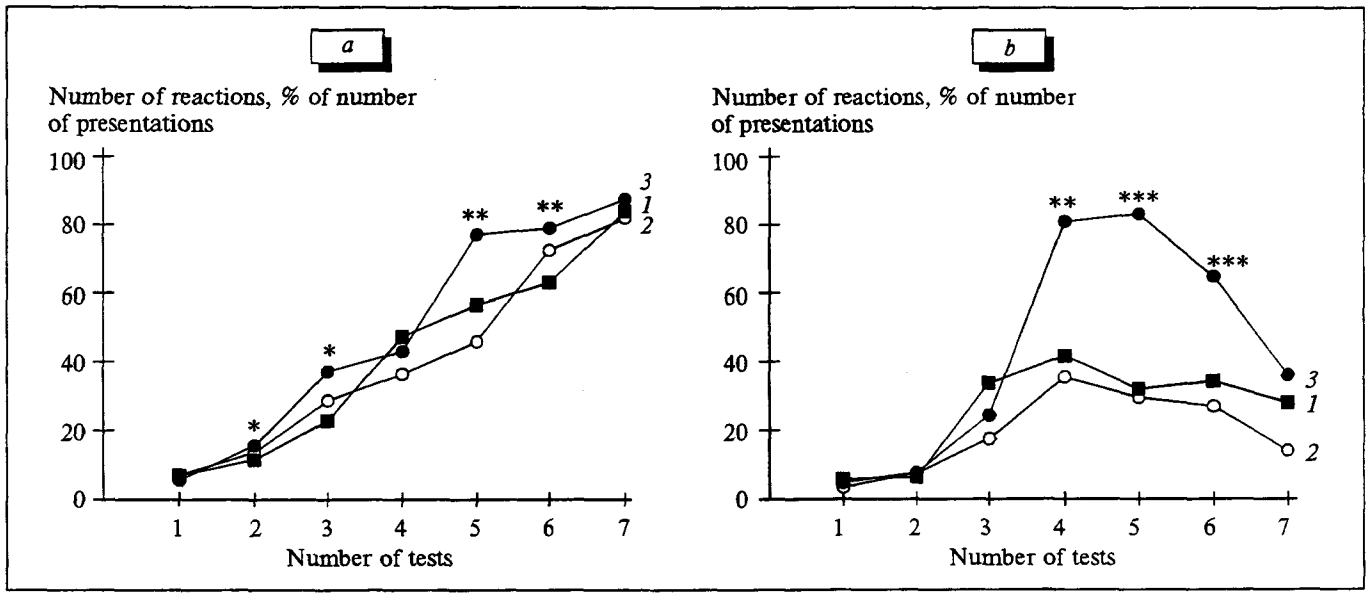


**Fig. 1.** Effect of PION−6 and piracetam on formation of AR (*a*) and intertrial reactions (*b*). *1*) control; *2*) piracetam, *3*) PION−6. *$p<0.05$, **$p<0.01$, ***$p<0.001$ compared with the control.

ously [4]. According to this method, the reaction of animals did not lead to switching off of the stimuli and the rats were shocked unexpectedly, this being repeated on three runs. The current was switched off immediately after the 3rd run, but the sound was discontinued only 2 sec later. After that on the same day the AR level was tested (20 presentations) under routine experimental conditions.

The experimental data were processed statistically by Wilcoxon and Kolmogorov-Smirnov's nonparametric tests.

## RESULTS

As is clear from the data in Fig. 1, AR formation is improved against the background of the test PP derivative as compared to the control. It should be noted that the test compound induced a more rapid relative increase of the number of intertrial reactions, which sharply decreased after the 5th day. According to the Pavlovian school of thought such a dynamics of intertrial reactions attests to speedier processes of generalization and specialization of a conditioned reflex. This general regularity, when applied to the conditioned defense reflexes, is expressed in a proportional rise of intertrial reactions and reactions of avoidance and escape at the initial stage [2,3,9]. In accordance with the mentioned theoretical considerations, the data obtained on the dynamics of intertrial reactions against the background of the test compound yield additional information concerning its stimulatory action.

It is also known that an increase of intertrial reactions attests to activation of the motivational component of the conditioned reflex and to an increase of the adaptive reserve of the organism [6]. The effect of the compound on the emotional sphere may be judged by the increase in the amount of fecal pellets.

On the last experimental day AR attained 80% of the level of learning in all animals, so that the AR values did not differ significantly among the tested groups (Fig. 1, *a*). The failure of AR was tested against this background. The data obtained are given in Table 1. The values of AR and intertrial reactions before and after malfunction are expressed in percent of the number of presentations. Since disturbances are mostly manifested immediately after malfunction and then the conditioned reaction is normalized [4], the entire test

**TABLE 1.** Effect of Piracetam and PION−6 on the AR Malfunction (in % of Number of Presentations, $M \pm m$)

| Substance | Prior to malfunction | After malfunction | | | |
|---|---|---|---|---|---|
| | | 1-5 | 6-10 | 11-15 | 16-20 |
| Physiological saline | 100 | 66.7±6.7 | 66.7±6.7 | 70.0±8.6 | 86.7±8.4 |
| Piracetam, 300 mg/kg | 100 | 80.0±5.4* | 90.0±3.8* | 90.0±3.8* | 97.5±2.5* |
| PION−6, 20 mg/kg | 92.0±3.3* | 88.0±4.4* | 86.0±6.0* | 86.0±4.3* | 90.0±4.5* |

**Note.** * denotes reliability ($p<0.05$) of differences as compared to the control.

period is divided into shorter intervals and all the values are given for a block of the last 5 presentations prior to malfunction and for blocks 1-5, 6-10, and so on after malfunction. As is evident from Table 1, the malfunction resulted in a reliable disturbance of the AR formed in the control animals. The number of intertrial reactions increased simultaneously, pointing to an increase of pragmatic indeterminacy and an increase of emotional stress [8]. This is in agreement with previous data, according to which a disturbance of the unambiguity of cause-effect relationships (the foundation of the present techniques) results in malfunction of higher nervous activity and in impaired elaboration and restoration of th AR [1,4,9]. Therefore, the findings attest to the development of acute emotional stress, creating appropriate conditions for a study of the adaptogenic action of psychotropic drugs.

The malfunction-induced destruction of AR restoration was less pronounced against the background of piracetam and the test compound then in control animals. The differences in AR restoration after malfunction in experimental animals and control rats became significant (Table 1). The restoration of the AR against the background of the test compound was higher then in control animals over the course of the test period.

It is shown that the test PP derivative exerts a psychostimulatory effect expressed in speedier learning during AR formation in a shuttle box. This compound exhibits an adaptogenic action comparable to the effect of piracetam on the model of acute emotional stress induced by disturbance of the unambiguity of cause-effect relationships.

The data obtained hold promise for the search and further experimental study of pyridopyrimidines as new psychotropic drugs with stimulatory action.

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