# PHARMACOLOGICAL CHARACTERISTICS OF 4-PHENYLPIRACETAM — A NEW PHENYL ANALOG OF PIRACETAM

Yu. G. Bobkov, I. S. Morozov,
O. M. Glozman, L. N. Nerobkova,
L. A. Zhmurenko, and V. A. Zagorevskii

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Previously we reported the anticonvulsant activity of some new pyrrolidone derivatives [1]. The most active of the compounds studied was found to be the amide of 4-phenylpyrrolidone-2-acetic acid, known as 4-phenylpiracetam. This paper gives data on the pharmacological properties of this compound, which possesses high biological activity. Drugs with a known spectrum of action were chosen for comparison — pyrrolidone derivatives, piracetam, and morpholep* [3, 8].

## EXPERIMENTAL METHOD

Experiments were carried out on male albino rats and mice weighing 180-200 and 16-18 g, respectively, and also on guinea pigs weighing 250-300 g. In experiments on mice the sedative, anticonvulsant, muscle-relaxant, and antiaggressive action of the above-mentioned compounds were investigated by known methods of pharmacological screening [11]. Acute 24-hourly toxicity after intraperitoneal injection was extimated by the method described previously [10]. The anticonvulsant action of 4-phenylpiracetam also was compared with that of morpholep in chronic experiments on eight rats with a cobalt epileptogenic focus in the motor cortex [7, 9], and with recording of electrical activity in the ipsilateral area of the cortex, the dorsal hippocampus, and anterior thalamus. The action of 4-phenylpiracetam in preventing

*Morsuximide.

TABLE 1. Central Neurotropic Depressant Action of the Compounds Tested (in $ED_{50}$ mg/kg with confidence interval at $P < 0.05$)

| Test | 4-Phenyl-piracetam | Piracetam | 4-Phenyl-pyrrolidone | Morpholep |
|---|---|---|---|---|
| Climbing on the netting (investigative behavior) | 382 (344—420) | Not det. | 64 (57—71) | 50 (20—80) |
| Rotating rod | 455 (396—514) | » | 124 (92—156) | 270 (263—287) |
| Maximal electric shock | 50 (30—70) | » | 127 (105—149) | 55 (48—63) |
| Antagonism with convulsant action of metrazol | 300 (113—487) | » | 168 (132—204) | 65 (42—88) |
| Suppression of evoked aggressiveness | 366 (210—522) | » | 88 (52—124) | 120 (97—143) |
| Acute 24-hourly toxicity ($LD_{50}$ in mg/kg by intraperitoneal injection) | 1100 (850—1430) | >10 000 | 352 (280—442) | 480 (472—488) |

Legend. Limits of variations shown in parentheses.

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TABLE 2. Effect of 4-Phenylpiracetam, Piracetam, and 4-Phenylpyrrolidone on Post-rotational Nystagmus in Guinea Pigs

| Experimental conditions | 4-Phenylpiracetam | | Piracetam | | 4-Phenylpyrrolidone | | Physiological saline (control) |
|---|---|---|---|---|---|---|---|
| | 50 mg/kg | 100 mg/kg | 50 mg/kg | 100 mg/kg | 50 mg/kg | 100 mg/kg | |
| Before injection of drug | 47 ± 5 | 45 ± 5 | 46 ± 7 | 40 ± 5 | 42 ± 4 | 49 ± 7 | 44 ± 6 |
| After injection of drug | 34 ± 3* | 30 ± 4* | 38 ± 6 | 31 ± 6 | 36 ± 5 | 33 ± 6 | 46 ± 7 |

Legened. Number of nystagmoid movements after stopping rotation (mean with standard error mean); *) values differing statistically significantly from corresponding values before injection of drug ($P < 0.05$).

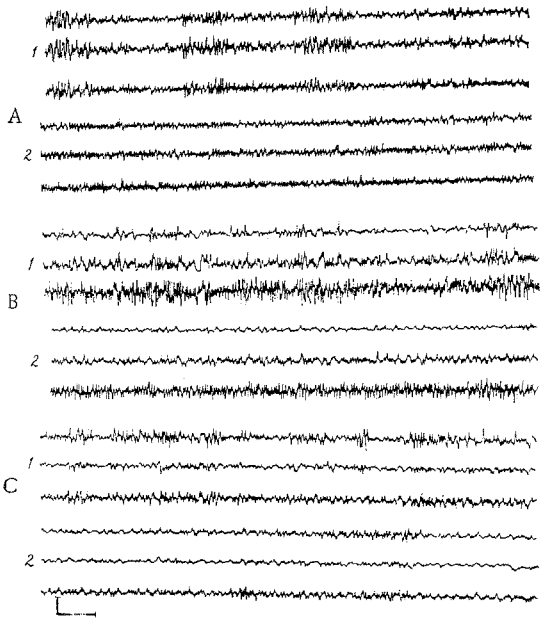


Fig. 1. Effect of 4-phenylpiracetam and morpholep on epileptiform activity in sensomotor cortex, thalamus, and hippocampus of rats induced by cobalt implantation. A: 1) Before, 2) after injection of 4-phenylpiracetam in a dose of 20 mg/kg; B: 1) before, 2) after injection of 4-phenylpiracetam in a dose of 100 mg/kg; C: 1) before, 2) after injection of morpholep in a dose of 20 mg/kg. On each trace, from top to bottom: electrical activity in sensomotor cortex ipsilateral relative to focus of seizure activity, anterior thalamus, and dorsal hippocampus. Recorded 60 min after injection of drug. Calibration: 50 μV, 1 sec.

motion sickness was compared with that of piracetam and 4-phenylpyrrolidone in experiments on 24 guinea pigs, using the inhibition of postrotational nystagmus test, with recording of the electro-oculogram [2]. The so-called nootropic action of 4-phenylpiracetam, and also of 4-phenylpyrrolidone and piracetam itself, was determined in mice as reflected in the degree of prevention of amnesia (the animals were taught to avoid the dark chamber) after electric shock [6]. The effect of 4-phenylpiracetam was compared with that of 4-phenylpyrrolidone and piracetam on the quality and character of active avoidance of painful electrical stimulation by Sidman's method in trained rats (36 animals). Full details of the technique used were described previously [4, 5]. The same method also was used to study the effect of 4-phenylpiracetam, and also of 4-phenylpyrrolidone and piracetam on the psychodepressant action of diazepam. All compounds were injected intraperitoneally 40-60 min before the experiments began.

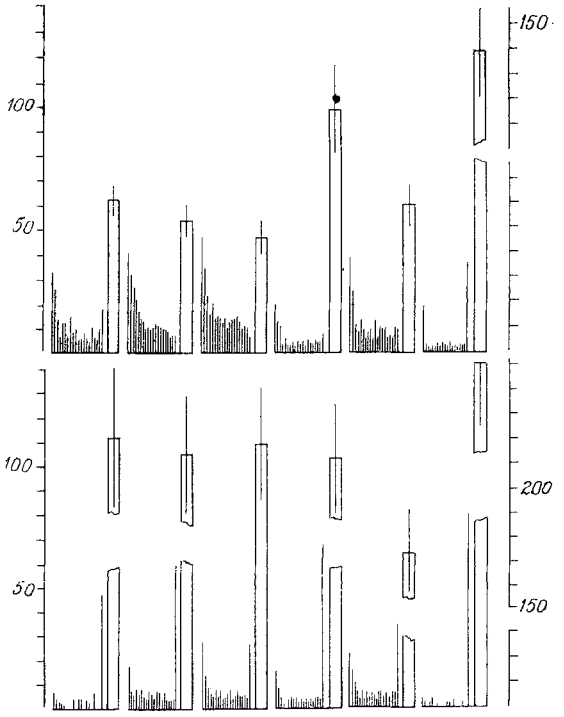


Fig. 2. Effect of 4-phenylpiracetam, piracetam, and 4-phenylpyrrolidone on operant activity of rats during active avoidance of painful electical stimulation without extraoceptive prevention, and also on psychodepressant effects of diazepam, determined by the same test (interval histograms shown on left) and the number of missed electric shocks (columns on the right). 1) Initital operant activity (injection of physiological saline); 2, 3, 4) 4-phenylpiracetam in doses of 10, 20, and 200 mg/kg, respectively; 5) piracetam 200 mg/kg (single dose); 6, 7) 4-phenylpyrrolidone in doses of 10 and 20 mg/kg, respectively; 8) diazepam 5 mg/kg; 9) diazepam 5 mg/kg and 4-phenylpiracetam 20 mg/kg; 10) diazepam 5 mg/kg and piracetam 200 mg/kg (single dose); 11) piracetam 100 mg/kg twice a day for 3 days and diazepam 5 mg/kg (single dose); 12) diazepam 5 mg/kg and 4-phenylpyrrolidone 10 mg/kg. Scale on left is both for histograms and for number of missed electric shocks; scale on right is for broken columns showing number of missed electric shocks.

## EXPERIMENTAL RESULTS

Data on the central neurotropic activity of depressant type of the various compounds are given in Table 1. They show that 4-phenylpiracetam has weak nonspecific psychodepressant action when given in large doses. However, this compound possesses high selective activity according to the maximal electric shock test. Piracetam did not exhibit activity according to the maximal electric shock test. Piracetam did not exhibit activity in these tests, but 4-phenylpyrrolidone had a marked nonselective psychodepressant action. Morpholep exhibited high anticonvulsant activity and inhibited investigative behavior. Piracetam was the least toxic and 4-phenylpyrrolidone the most toxic compound.

The effect of 4-phenylpiracetam and morpholep on epileptiform activity in the sensomotor cortex, hippocampus, and thalamus arising after implantation of cobalt is shown in Fig. 1. Inhibition of seizure discharges in these structures was observed after injection of 4-phenylpiracetam in a dose of 20 mg/kg (Fig. 1A). Injection of this compound in a dose of 100 mg/kg (Fig. 1B) caused almost total suppression of epileptiform activity in the cortex and thalamus. Seizure discharges in the hippocampus were reduced under these circumstances but did not disappear completely. The effect observed lasted 5 h or longer. Morpholep in a dose of 20-30 mg/kg had a weaker action on the epileptiform manifestations (Fig. 1C). The compound with the greatest activity in the suppression of postrotational nystagmus test was 4-phenylpiracetam, that with the least activity was 4-phenylpyrrolidone (Table 2).

During investigation of the so-called nootropic, or antiamnesic, action it was found that after injection of physiological saline before learning to avoid the dark chamber, followed by electric shock, the next day 22 of the 24 mice went into the dark chamber. If 4-phenylpiracetam,

piracetam, and 4-phenylprrolidone were given under similar conditions in a dose of 80 mg/kg, the number of times the animals went into the dark chamber was 4, 8, and 9 of 24, respectively. Consequently, 4-phenylpiracetam can also prevent the development of amnesia induced by electric shock.

As Fig. 2 shows, 4-phenylpiracetam in small doses (10 and 20 mg/kg) had an optimizing effect on the type of operant behavior studied. After injection of 4-phenylpiracetam the number of short intervals between pressing the pedal (1-2 sec) and the total number of presses on the pedal increased, whereas the number of missed electric shocks decreased. In a large dose 4-phenylpiracetam inhibited this type of goal-directed activity. Over the whole range of doses used, 4-phenylpyrrolidone resulted in worse ratings of operant activity and exhibited a marked psychodepressant action, whereas piracetam itself had no effect in this test. A single dose of piracetam had no effect, whereas a dose of 100 mg/kg given twice a day for 3 days before diazepam (5 mg/kg) reduced the manifestations of the psychodepressant action of this tranquilizer a little. In a dose of 20 mg/kg, even if given only once, 4-phenylpiracetam corrected the psychodepressant effects of diazepam, but 4-phenylpyrrolidone potentiated them over the whole range of doses used.

The results are evidence that 4-phenylpiracetam, the new phenyl derivative of piracetam, possesses a unique spectrum of action: In small doses this compound exhibits elements of psychostimulant (nootropic) action, whereas in large doses it inhibits behavioral responses. The mechanism of the psychostimulant action of 4-phenylpiracetam may perhaps be analogous to that of piracetam [8]. The unique combination of the neurotropic action of stimulant type and anticonvulsant properties described above may be explained by the ability of this compound to reduce excitability of motor cortical neurons selectivity, as is confirmed to some extent by the data given above showing the weak effect of 4-phenylpiracetam on seizure discharges in the hippocampus.

## LITERATURE CITED


1. O. M. Glozman, I. S. Morozov, L. A. Zhmurenko, et al., Khim. Farm. Zh., No. 11, 43 (1980).
2. N. Ya. Lukomskaya and M. I. Nikol'skaya, The Search for Remedies against Motion Sickness [in Russian], Leningrad (1971).
3. I. S. Morozov, "Effect of neuroactive amino acids and their derivatives on mechanisms of vascular regulation," Author's Abstract of Candidate's Dissertation, Moscow (1975).
4. I. S. Morozov, Farmakol. Toksikol., No. 5, 540 (1980).
5. I. S. Morozov and D. D. Pukhov, Byull. Eksp. Biol. Med., No. 10, 500 (1979).
6. R. Ader, J. A. W. M. Weijnen, and P. Moleman, Psychol. Sci., 26, 125 (1972).
7. R. Dow, A. Fernandez-Guardiola, and E. Nianni, Electroencephalogr. Clin. Neurophysiol., 14, 339 (1962).
8. C. Giurgea, Actual. Pharmacol., 25, 115 (1972).
9. L. M. Kopeloff, Proc. Soc. Exp. Biol. (New York), 104, 500 (1960).
10. G. T. Litchfield and F. G. Wilcoxon, J. Pharmacol. Exp. Ther., 96, 99 (1949).
11. A. Turner, in: Screening Methods in Pharmacology, New York (1965), p. 283.