Antidepressant Activity of Aspartic Acid Derivatives

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Antidepressant activity of N-phenyl(benzyl)amino derivatives of aspartic acid was studied on various experimental models of depression. IEM-1770 (30 mg/kg) and IEM-1944 (20 mg/kg) exhibited antidepressant activity after single injection in the forced swimming and tail suspension tests. Antidepressant effect of 14-day administration of these compounds and reference drugs maprotiline (10 mg/kg) and citalopram (10 mg/kg) was confirmed on the model of learned helplessness.

Key words: *excitatory amino acids; antidepressants*

Drugs acting via excitatory amino acids attracted much recent attention as potential psychotropic preparations. The key role of transmitter amino acids in the regulation of important physiological functions in the body necessitates the search for new effective drugs among these compounds and their derivatives. It was found that some acyl derivatives of aspartic acid possess nootropic, stress-protective, and antidepressant activity [2,4,6].

The aim of the present study was to evaluate antidepressant effects of single or chronic administration of phenyl(benzyl)amino derivatives of DL-aspartic acid on various models of experimental depression.

MATERIALS AND METHODS

Antidepressant activity was evaluated using a modified forced swimming test [8,10]: the duration of immobilization, swimming, and active avoidance in trained rats were recorded for 300 sec.

In addition, the tail suspension test was used [11]. The test was carried our in a chamber (60×25×20) divided into two halves (30 cm each). A mouse was suspended with a plaster adhered to the tail 1.5 cm away from the tip. The duration of immobilization (motionless hanging) was recorded for 6 min simultaneously in 2 animals.

The effect of test drugs on motor activity and orientatation exploratory behavior was examined in the open field test.

Effect of chronic (14 days) administration of test drugs was examined on the model of stress-induced experimental depression model (learned helplessness) [9]. The rats were subjected to two-week unavoidable stress including immobilization and nociceptive electrical stimulation. Each animal was placed into a small cage, the electrodes were fixed on the tail outside the cage. The stimulation (n=100, stimulus duration 5 sec, interval between stimuli 60 sec) started with 1 mA and increased by 0.2 mA in each 20 stimuli.

After 14-day stress the animals were daily intraperitoneally injected with 30 mg/kg IEM-1770, 20 mg/kg IEM-1944, 10 mg/kg maprotiline, or citalopram (10 mg/kg). Control animals were injected with physiological saline. The state of stressed animals was evaluated during stress and after injections.

Emotional state was evaluated by depressive behavior score [3]. The following parameters were analyzed: water consumption, preference for sucrose over water, immobilization time in the forced swimming test, depression index, and loss of body weight. In addition, zoosocial interaction test [5] was used for complex evaluation of emotions, motivation, and interspecies behavior. It consisted of three sessions: before experiments, after stress, and after drug treatment.

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The results were processed statistically by Student's *t*, Newman—Keuls, and Wilcoxon pair tests using Microsoft Excel 97 and Biostatistics 4.03 software.

RESULTS

Forced swimming test showed that IEM-1944 in doses of 20, 30, and 50 mg/kg and IEM-1770 in doses of 30 and 50 mg/kg markedly shortened immobilization time and prolonged the time of active avoidance (Fig. 1).

IEM-1770 (30 mg/kg) and IAM 1944 (20 mg/kg) significantly decreased immobilization time in mice, and their effect surpassed the effect of imipramine (Table 1).

Test drugs had no effect on motor activity in the open field test. This points to their selective antidepressant, rather than general psychostimulatory effect.

In control animals receiving physiological saline, the depressive state persisted for 2 weeks after 2-week stress as evidenced by insignificant decrease in the total behavioral depression score by the end of the experiment (Table 2). In this group, the time of immobilization slightly decreased, but sucrose preference continued to decrease, which attested to persistent hedonic disorders. Citalopram significantly decreased the total depression score, while maprotiline was less ef-

TABLE 1. Antidepressant Activity of Test Drugs in Tail Suspension Test (*M*±*m*)

Experiment	Immobilization time	
	abs., sec	%
Control	151.2±15.8	100
IEM-1770, 30 mg/kg	92.3±16.4*	61*
IEM-1944, 20 mg/kg	83.5±19.8*	55*
Imipramine, 10 mg/kg	105.1±23.4*	69

Note. *$p<0.05$ compared to the control group (Student's *t* test).

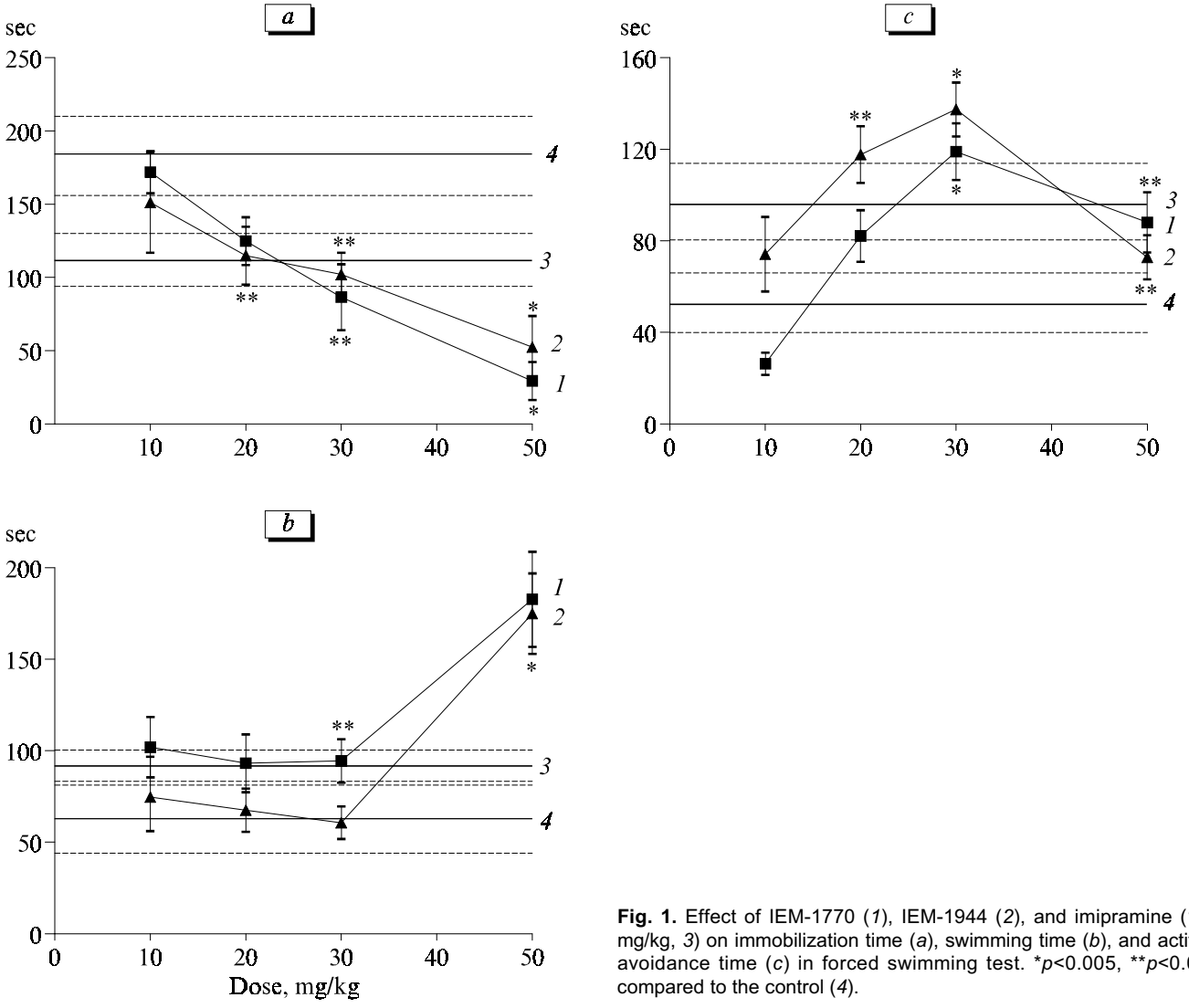

Fig. 1. Effect of IEM-1770 (*1*), IEM-1944 (*2*), and imipramine (10 mg/kg, *3*) on immobilization time (*a*), swimming time (*b*), and active avoidance time (*c*) in forced swimming test. *$p<0.005$, **$p<0.05$ compared to the control (*4*).

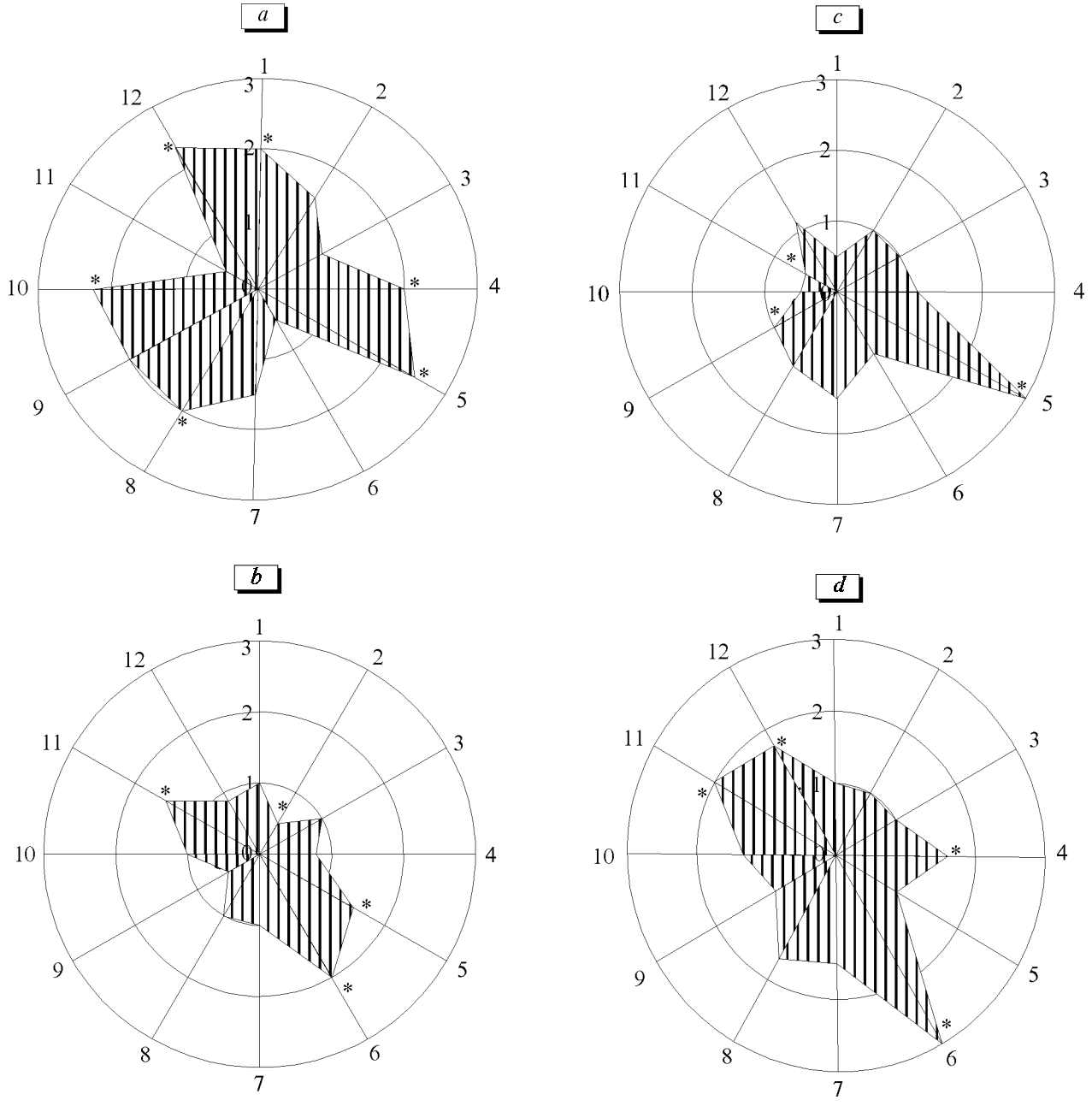

Fig. 2. Effect of maprotiline (10 mg/kg, *a*), citalopram (10 mg/kg, *b*), IEM-1770 (30 mg/kg, *c*), and IEM-1944 (20 mg/kg, *d*) on emotional behavioral reactions in zoosocial interaction test. *$p<0.05$ compared to the state after stress (nonparametric Wilcoxon test for repeated measurements). Axes: *1*) aggression; *2*) anxiety; *3*) negativism; *4*) exploratory behavior; *5*) self-maintenance; *6*) benevolence; *7*) comfort; *8*) motivation expression; *9*) inadequacy of behavior; *10*) conflicts; *11*) sociability; *12*) somatomotor elements of behavior. Data are presented as the score after treatment compared to that after stress.

fective in restoring animal behavior. Test drugs IEM-1770 and IEM-1944 showed antidepressant effect similar to that of citalopram and decreased the total depression score to 3.6 and 3.2, respectively (Table 2).

Aspartate derivatives and reference drugs improved animal behavior and decreased depression index in the forced swimming test. Moreover, IEM-1770 and IEM-1944 markedly shortened the duration of immobilization. At the same time, citalopram did not increase sucrose consumption, while maprotiline even decreased it. In contrast to reference drugs, IEM-1770 increased sucrose preference under conditions of free choice.

Zoosocial interaction test showed that long-term stress increased agressiveness (2.0), anxiety (1.5), decreased intraspecies communication and benevolence, and disturbed motivations. In control animals receiving physiological saline for 14 days, emotional and motivation parameters remained unchanged.

TABLE 2. Estimation of Animal Behavior by Integral Depression Score ($M \pm m$, According to Depression Scale [3])

Parameter	Before treatment	After treatment				
		control (physiological saline)	maprotiline, 10 mg/kg	citalopram, 10 mg/kg	IEM-1770, 30 mg/kg	IEM-1944, 20 mg/kg
Decrease in water consumption	0.9±0.3	0.8±0.4	1.0±0.4	0.6±0.4	1.0±0.4	0.8±0.5
Decrease in sucrose preference	1.4±0.4	2.0±0.4	1.4±0.6	1.2±0.8	1.0±0.5	1.4±0.4
Immobilization time	2.0±0.6	1.4±0.3	0.8±0.2*	1.0±0.7	0.4±0.4*	0*
Depression index	1.1±0.4	1.0±0.4	0*	0.2±0.2*	0.2±0.2*	0*
Body weight loss	1.1±0.5	1.0±0.4	1.0±0.6	0.4±0.4	1.0±0.6	1.0±0
Total score	6.5±0.8	6.2±0.5	4.2±0.2*	3.4±0.8*	3.6±0.7*	3.2±0.5*

Note. Since no significant differences between animal groups were found before treatment, the mean values for all animals were pooled. *$p<0.05$ compared to the control group (Newman—Keuls test for multiple comparisons).

Maprotiline treatment increased aggressiveness (2.0), induced conflicts during communication (2.25), and increased anxiety (1.5), which agrees with published data [1,7]. Our experiments also revealed that maprotiline enhanced exploratory activity (2.0) and somatomotor elements of behavior (2.33; Fig. 2).

In contrast to maprotiline, citalopram did not increase aggressiveness, but improved emotional state and increased sociability (1.5) and benevolence during communication (2.0). It also decreased anxiety (0.5) and increased self-maintenance (1.5).

IEM-1770 significantly increased self-maintenance (3.0) and parameters of comfort behavior (1.5), decreased aggressiveness (0.5), but also decreased total number of contacts with the partner.

IEM-1944 increased sociability (2.0) and benevolence (3.0). Moreover, it produced a positive effect on some parameters of individual behavior increasing motivation expression (1.67), comfort (1.75), exploratory activity (1.6), and somatomotor elements of behavior (1.5). IEM-1944 had no effect on anxiety (1.0) and aggressiveness (1.0; Fig. 2).

Thus, new aspartate derivatives produced an antidepressant effect in the forced swimming and tail suspension tests, and their effect surpassed the effect of imipramine. Antidepressant properties of IEM-1770 (30 mg/kg) and IEM-1944 (20 mg/kg) after 14-day administration were confirmed by decreased total depression score after 14-day unavoidable stress. Zoosocial interaction test showed that these drugs increased motivation elements in rats with experimental depression.

REFERENCES

1. L. Allikmets, *Fundamental Studies as a Base for Creation of Pharmacological Drugs* [in Russian], Volgograd (1995).
2. I. A. Grigor'ev, *Psychopharmacology of the New Class of Nootropics, Neurotransmitter Amino Acid Derivatives Acting via EAA-ergic mechanisms.* Abstract of Doct. Med. Sci. Dissertation, Volgograd (1998).
3. N. A. Krupina, I. N. Orlova, and G. N. Kryzhanovskii, *Zh. Vyssh. Nervn. Deyat.*, **49**, No. 5, 864-875 (1999).
4. V. I. Petrov and I. A. Grigor'ev, *Vestn. Ross. Acad. Med. Nauk*, No. 11, 29-35 (1998).
5. V. I. Petrov, I. A. Grigor'ev, and S. G. Gorbunov, *Eksp. Klin. Farmakol.*, **59**, No. 4, 65-69 (1996).
6. A. V. Sabanov, *Pharmacological study of the efficacy and action mechanisms of new neurotransmitter amino acid derivatives during experimental alcoholism*, Abstract of Cand. Med. Sci. Dissertation, Volgograd (1996).
7. M. G. Cutler, R. J. Rodgers, and J. E. Jackson, *Pharmacol. Biochem. Behav.*, **57**, 119-125 (1997).
8. M. J. Detke and I. Lucki, *Behav. Brain Res.*, **73**, 43-46 (1996).
9. F. Petty, G. Kramer, and L. A. Wilson, *Pharmacol. Biochem. Behav.*, **43**, 361-367 (1992).
10. R. D. Porsolt, M. Le Pichon, and M. Jalfre, *Nature*, **266**, No. 21, 730-732 (1977).
11. L. Steru, R. Chermat, B. Tierry, *et al., Psychopharmacology,* **85**, 367-370 (1985).