"DESPAIR" AND "ESCAPE" BEHAVIORAL TESTS IN ANTIDEPRESSANT EVALUATION

V. A. Parshin, S. M. Golovina,
and N. I. Andreeva

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Rats and mice swimming in cylinders filled with water have recently been used as a test for the experimental study of antidepressant activity [12]. The animals in water soon cease their unsuccessful attempts to jump out of the cylinder and perform only the small movements which enable them to keep their head above the water. This state of immobilization is interpreted as a state of depression, or of "despair" behavior. Antidepressants reduce the duration of immobilization by increasing the animals' active attempts to jump out of the water [7, 10, 12, 13].

Japanese workers have suggested a modification of this method [11]. Mice are placed in plastic boxes filled with water, containing a paddle wheel, by rotating which the mice attempts to jump out of the water. The number of rotations of the wheel is recorded by a counter. In this case the animals' active behavior is described as "escape" behavior. According to the authors cited [11] this effect is more specific for antidepressants than for psychostimulants and other drugs increasing motor activity in general.

In the investigation described below, activity of the Soviet antidepressants pyrazidol (pirlindol) and inkazan was studied with reference to these two parameters and compared with the activity of nialamide, imipramine, nomifensine, and mianserin.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male and female albino mice weighing 16-18 g. The antidepressants were given internally as a single dose or repeatedly for 5 days. The mice were placed in cylinders 10 cm in diameter and 25 cm high [12] or in a plastic box measuring 20 × 8 × 18 cm [11], filled with water, and containing a rotating paddle wheel, 60 min after the last (or only) dose of the drugs. The temperature of the water in method [12] was 21-23°C and in method [11] 25°C. In the experiments by the first method the number and duration of immobilizations (giving up swimming movements) during the first 6 min were recorded, whereas in the tests by the second method the number of rotations of the wheel during the 1st and 2nd periods of 6 min after immersion of the mice in water was counted.

EXPERIMENTAL RESULTS

In the "despair" behavioral swimming tests all the antidepressants used shortened the duration of immobilization of the mice (Table 1). Their effect was quite similar. Pyrazidol, inkazan, nialamide, and mianserin, in a dose of 25 mg/kg, shortened the period of immobilization of the animals to 81-88% compared with the control (100%). In a dose of 10 mg/kg they had no significant effect on the duration of immobilization.

Imipramine shortened the duration of immobilization to 84% in a dose of 10 mg/kg and to 70% in a dose of 25 mg/kg. Nomifensine was the most active of all the compounds studied. In a dose of 5 mg/kg it shortened immobilization to 44%.

When the antidepressants were given over a period of 5 days their effect was stronger than that of a single dose (Table 1).

Similar results were observed in the "escaping" behavioral test. During the first 6 min after immersion of the mice in water their ability to escape actively from the water by turning the paddle wheel was changed only a little by the antidepressants. After a single

S. Ordzhonikidze All-Union Pharmaceutical Chemical Research Institute, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR M. D. Mashkovskii.)
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TABLE 1. Effect of Antidepressants on Duration of Immobilization in "Despair" Swimming Behavior Test (M ± m)

Preparation	Dose, mg/kg	Duration of immobilization (in sec) for one mouse during first 6 min after immersion in water			
		single dose		administration for 5 days	
Distilled water (control)	—	167±6,1	(60)	166±9,0	(40)
Pyrazidol	10	155±5,9	(40)	142±5,7***	(30)
	25	137±9,9***	(40)	116±8,1*	(30)
Inkazan	10	159±6,8	(20)	143±8,2	(30)
	25	147±7,7***	(30)	131±6,8**	(30)
Nialamide	10	150±10,3	(20)	137±9,5***	(20)
	25	137±6,1**	(20)	128±10,4**	(20)
Imipramine	10	140±5,9**	(30)	98±5,9*	(20)
	25	117±6,8*	(30)	60±6,3*	(20)
Mianserin	25	135±11,3***	(30)	105±8,9*	(20)
Nomifensine	5	73±9,0*	(20)	55±13,5*	(20)

TABLE 2. Effect of Antidepressants on Ability of Mice to Actively "Escape" from Water in Swimming Test (M ± m)

Preparation	Dose, mg/kg	Number of rotations of paddle wheel during 2nd period of 6 min after immersion in water			
		single dose		administration for 5 days	
Distilled water (control)	—	2,8±0,4	(40)	2,6±0,5	(30)
Pyrazidol	10	3,6±0,5	(30)	5,4±1,4***	(20)
	25	5,7±0,83**	(50)	7,5±2,0**	(20)
Inkazan	10	3,6±0,97	(20)	4,1±0,6**	(20)
	25	4,7±0,63***	(50)	7,0±0,9*	(20)
Nialamine	10	3,7±0,7	(30)	5,9±1,0*	(20)
	25	5,9±1,7**	(50)	7,7±1,0*	(20)
Imipramine	10	5,0±0,81**	(50)	—	
Mianserin	25	5,0±0,97***	(30)	7,7±3,0*	(20)
Nomifensine	5	9,7±1,2*	(30)	—	

Legend. Here and in Table 2: *p < 0.001, **p < 0.02, ***p < 0.05 compared with control; number of animals given in parentheses.

dose, only nomifensine increased this ability. However, in the second period of 6 min all the antidepressants had an activating effect. Just as in the first test, pyrazidol, inkazan, nialamide, and mianserin were effective in a dose of 25 mg/kg, but in a dose of 10 mg/kg they virtually did not increase the animal's activity. Imipramine caused activation of the mice in in a dose of 10 mg/kg also. Nomifensine in a dose of 5 mg/kg had the strongest activating action.

During repeated administration of the antidepressants, their effect on "escaping" behavior also was increased (Table 2).

The investigation showed that the antidepressants studied has a similar effect in both behavioral tests. They shortened the duration of immobilization of the mice in the "despair" test on account of an increase in the number of active attempts to jump out of the water, recorded by means of the paddle wheel in the "escaping" test. Since the activity of the compounds tested in this way was comparable with their activity in antidepressive tests such as interaction with reserpine, clofelin, and apomorphine [2], a definite role can be ascribed to behavioral swimming tests during screening of potential antidepressants. The test in which the number of rotations of a paddle wheel is recorded (the "escaping" test) is more accurate and also enables a larger number of compounds to be tested. Incidentally, antidepressants with a catecholaminergic component of their action are more active in these tests than antidepressants with a predominantly serotoninergic action, whose effect is weaker [6, 8, 9, 11, 14, 15].

Pyrazidol and inkazan exert their effects more on serotoninergic than on catecholaminergic systems [1-5]. This may account for their weaker activating action on "escaping" behavior than that of imipramine and, in particular, of nomifensine. The data obtained for imported antidepressants agreed with those given by other workers [6, 9, 14].

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MECHANISMS OF RETINAL DAMAGE IN CHLOROQUINE RETINOPATHY

T. A. Ivanina, M. N. Lebedeva, N. L. Sakina, M. A. Babizhaev, and V. N. Ermakova

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Chloroquine, which is widely used in clinical practice for the treatment of malaria and autoimmune diseases, if used for a long time can cause degeneration of the retina [4, 6, 8]. Previously the authors showed [3, 9] on a model of chloroquinine-induced retinal degeneration that the outer segments (OS) of the photoreceptors are most vulnerable to the action of chloroquine and were destroyed virtually completely. According to other investigators certain antimalarial drugs and, in particular, primaquine, exert their damaging action on the malarial parasite by a mechanism of lipid peroxidation (LPO) [5]. Considering that the phospholipids of the membranes of OS contain mainly polyunsaturated fatty acids, which are extremely sensitive to peroxidation, it might be supposed that chloroquine retinopathy is also connected with LPO. No definite data are yet available, however, on chloroquine and its effect on LPO.

This paper describes comparative electron-microscopic, electrophysiological, and biochemical investigations of the effect of chloroquine on LPO in vivo (rats, rabbits) and in vitro (on model systems).

EXPERIMENTAL METHOD

Wister albino rats and pigmented rabbits were used. The rats were divided into three groups: animals of group 1 (control) received no drugs, animals of group 2 received chloro-

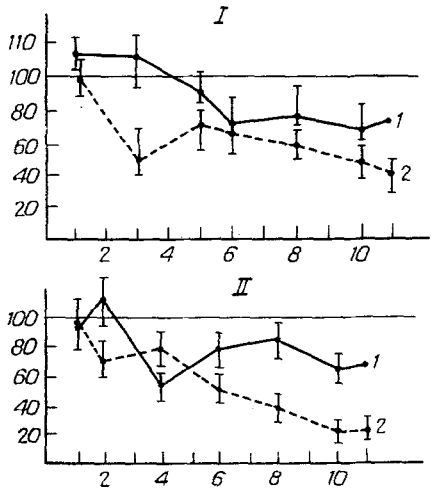

Fig. 1. Change in amplitude of a (I) and b (II) waves on ERG of rats during chronic administration of chloroquine. Abscissa, duration of administration of drug (in months); ordinate, amplitude of wave in % of control. 1) Chloroquine; 2) chloroquine + ionol.

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