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Effects of Neuroleptics Displaying Antidepressant Activity on Behavior of Rats in the Forced Swimming Test

ZBIGNIEW GÓRKA* AND KRZYSZTOF JANUS†

**Institute of Pharmacology, Polish Academy of Sciences, 31-343 Kraków*
†Institute of Environmental Biology, Jagiellonian University, 30-060 Kraków, Poland

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GÓRKA, Z. AND K. JANUS. *Effects of neuroleptics displaying antidepressant activity on behavior of rats in the forced swimming test.* PHARMACOL BIOCHEM BEHAV **23**(2) 203–206, 1985.—Levomepromazine, thioridazine and cis-chlorprothixene, neuroleptics with antidepressant activity, trans-chlorprothixene, the therapeutically inactive isomer of chlorprothixene, clozapine, an atypical neuroleptic, and imipramine, a classical antidepressant, were studied in the forced swimming test in rats after single or chronic administration. Levomepromazine (1.5 mg/kg), clozapine (2.5 and 5.0 mg/kg) and imipramine (10 mg/kg) after single administration, 1 hr before the test, shortened the period of the immobility. After chronic administration only imipramine (10 mg/kg orally, twice daily, for 10 days) diminished the immobility. Levomepromazine, thioridazine, cis-chlorprothixene and trans-chlorprothixene (1.5 mg, orally, twice daily, for 10 days), 15–18 hr after the last dose did not influence the immobility, although the behavioral parameters in the open field test were not depressed. It is concluded that the forced swimming test is not a suitable pharmacological model for revealing antidepressant activities of certain neuroleptics that are useful in treating certain forms of human depression.

Forced swimming test Rats Neuroleptics Imipramine

SOME neuroleptics (levomepromazine (LPZ), thioridazine (TRZ) and chlorprothixene (CPX)) appear to be effective in the treatment of subgroups of depressives [4, 8, 9, 11, 12, 15, 18, 19]. In pharmacological tests, apart from their antagonistic effects on dopaminergic and noradrenergic receptors [1, 10, 14], they have been shown to be serotoninolytics. When administered in doses much below the cataleptogenic range, these drugs inhibit the behavioral syndrome induced by 5-hydroxytryptamine [13].

Previously we have reported that the immobility period in the forced swimming test [16] may be shortened by antidepressant drugs with central antiserotonin activity [5], but not by serotonin-mimetics [6]. In this study we decided to determine if the forced swimming test in rats can discriminate between neuroleptics with and without therapeutic action in depression in man. Data on the effects of neuroleptics in the swimming test are conflicting [3, 16, 17]. Chlorpromazine, haloperidol and pimozide increase the immobility period [16,17], reserpine is ineffective [17], and clozapine and trans-chlorprothixene are reported to reduce the immobility [3]. In present experiments we investigated the effects of single and chronic administration of neuroleptics of different therapeutic and pharmacological profiles on behavior of rats in the forced swimming test. Reduction in immobility in this test is regarded as an indicator of a possible antidepressant action, and has been shown at dose levels which otherwise decrease activity in the open field test [16]. This suggests that reduced immobility is not a manifestation of a generalized increase in activity levels. Since neuroleptics depress locomotor activity, in this study the rats, after chronic treatment with LPZ, TRZ, cis-chlorprothixene (c-CPX) and trans-chlorprothixene (t-CPX), were also tested in the open field to evaluate the contribution of activity level to possible reductions in immobility.

METHOD

Male Wistar rats, 200–250 g, were housed ten to a cage (56×36×20 cm) under standard laboratory conditions, with free access to granulated food and tap water throughout the experiment. Drugs were administered either in a wide range of doses (0.1–15.0 mg/kg) intraperitoneally, 1 hr before the swimming test (in acute experiments), or in a dose of 1.5 mg/kg orally, twice daily (at 8 a.m. and 6 p.m.) for 10 days (in chronic experiments). Based on our previous results [5,6], imipramine (IMI) was administered only in one dose of 10 mg/kg in both acute and chronic regiments of treatment. The control groups received an equal volume of vehicle (4 ml/kg of double-distilled water) under the same conditions. The immobility period in the forced swimming test and behavioral parameters in the open field were determined on the 11th day 15–18 hr after the last dose. All rats were distributed

TABLE 1
EFFECTS OF ACUTE AND CHRONIC TREATMENT WITH NEUROLEPTICS ON THE IMMOBILITY IN THE FORCED SWIMMING TEST IN RATS

Treatment	Dose mg/kg	Acute Immobility sec Mean ± SEM	% control	Chronic Immobility sec Mean ± SEM	% control
Solvent				252.2 ± 5.9	100
LPZ	0	260.5 ± 9.3	100		
	0.5	259.2 ± 9.7	99.5		
	1.5	221.9 ± 8.3*	85.2	246.4 ± 8.4	97.7
	5.0	231.7 ± 14.2	88.9		
	15.0	254.7 ± 5.2	97.8		
TRZ	0	267.1 ± 9.3	100		
	0.5	264.0 ± 9.1	98.8		
	1.5	267.3 ± 10.9	100.1	261.2 ± 7.2	103.6
	5.0	273.7 ± 8.4	102.5		
	15.0	286.1 ± 8.2	107.1		
c-CPX	0	251.9 ± 12.9	100		
	0.1	247.2 ± 12.6	98.1		
	0.5	257.2 ± 7.5	102.1	252.0 ± 4.7	99.9
	2.5	255.1 ± 7.6	101.3		
	10.0	246.6 ± 9.9	97.3		
t-CPX	0	254.5 ± 11.5	100		
	0.1	260.8 ± 8.4	102.5		
	0.5	265.9 ± 8.2	104.5	247.0 ± 6.9	97.9
	2.5	249.2 ± 18.4	97.9		
	10.0	257.0 ± 7.7	101.0		
CIZ	0	260.4 ± 11.3	100		
	2.5	203.5 ± 14.9†	78.1		
	5.0	215.7 ± 8.5†	82.9		
	10.0	259.3 ± 10.2	99.6		
IMI	0	260.1 ± 10.6	100	269.1 ± 12.1	100.0
	10.0	226.0 ± 9.9*	86.9	235.7 ± 8.0*	87.6

In chronic experiments the neuroleptics were administered in a dose of 1.5 mg/kg (only IMI—10 mg/kg) orally, twice daily, for 10 days. Significance from control for LPZ and CIZ $F(4,34)=3.024$, $p<0.05$ and $F(3,32)=6.539$, $p<0.01$ (ANOVA), respectively, and for IMI $p<0.05$ (Student's t-test, two tailed).

for the experimental groups at random. Each group consisted of 9–10 rats. Each rat was tested only in one test.

The swimming test was performed on two consecutive days according to Porsolt *et al.* [16]. On the first day (the 10th day of the chronic treatment) the rats were individually placed in cylinders containing water 15 cm high at 25°C for 15 min. On the following day (11th day) the rats were again immersed in water and total duration of immobility was measured for 5 min.

In the open field test, ambulation, rearing, grooming and defecation were measured using the apparatus of the type described by Broadhurst [20]. The open field apparatus was a white wooden circular box (diameter 120 cm) with 45-cm-high walls. The floor was divided into the central area and eighteen sectors. Illumination was provided by a 100 W bulb placed 50 cm above the center of the field. At the beginning of the 3-min test one rat was placed in the center of the apparatus. During testing, ambulation was recorded as the duration of locomotor activity in seconds, and as the number of sections entered during the test period. Rearings were defined as the number of times the rat removed its fore-paws from the floor. Number of grooming episodes, and defecations (number of faecal boli excreted in 3 min) were also recorded. The walls and base of the apparatus were cleaned with distilled water after each test.

The following substances were used: levomepromazine (Egyt) (methotrimeprazine, USP), thioridazine (Polfa), cis-chlorprothixene (Lundbeck), and its therapeutically inactive isomer trans-chlorprothixene (Lundbeck), clozapine (Wander) and imipramine (Polfa), as a reference drug in the swimming test.

RESULTS

Immobility period and behavioral parameters in the open field are shown in Tables 1 and 2. The results were tested for statistical significance by the one-way analysis of variance and the Student-Newman-Keuls test. Single administration of LPZ (1.5 mg/kg), CLZ (2.5 and 5.0 mg/kg), and IMI (10.0

TABLE 2

EFFECTS OF CHRONIC TREATMENT WITH THE NEUROLEPTICS ON BEHAVIORAL PARAMETERS IN THE OPEN FIELD IN RATS

Treatment		Ambulation 1	Ambulation 2	Rearings 3	Grooming 4	Defecation 5
Solvent	Mean	75	39	16	3	3
	SEM	13	8	2	1	1
	%	100	100	100	100	100
LPZ	Mean	82	41	20	4	5
	SEM	8	7	1	1	1
	%	109	105	130	126	140
TRZ	Mean	67	36	19	2	3
	SEM	6	5	4	1	1
	%	90	91	121	71	102
c-CPX	Mean	69	34	14	3	5
	SEM	7	3	2	1	1
	%	92	88	88	96	141
t-CPX	Mean	65	29	13	3	3
	SEM	6	5	3	1	1
	%	86	73	82	106	100

The neuroleptics were administered in a dose of 1.5 mg/kg orally, twice daily, for 10 days. The test was performed 15–18 hr after the last dose. 1. Time of ambulation in seconds/3 min. 2. Number of sectors crossed/3 min. 3. Number of times animal removed forepaws from the floor/3 min. 4. Times animal groomed/3 min. 5. Numbers of faecal boli excreted/3 min. Mean values ± SEM of 9–10 rats.

mg/kg) shortened the immobility period in the forced swimming test. The statistical significance from the control values for LPZ and CLZ was $F(4,34)=3.024$, $p<0.05$ and $F(3,32)=6.539$, $p<0.01$ (ANOVA), respectively, and for IMI $p<0.05$ (Student's t-test, two tailed). After chronic administration only IMI diminished the immobility from 269.1±12.1 sec (100%) to 235.7±8.0 sec (87.6%), $p<0.05$ (Student's t-test, two tailed). None of the remaining drugs changed behavior of rats in the swimming test or in the open field situation.

DISCUSSION

The results indicate that for the neuroleptics with antidepressant effects in man, LPZ, TRZ and c-CPX, only LPZ after single administration shortened the immobility period in the forced swimming test. Neither TRZ nor c-CPX were active in the swimming test, in spite of administration of these drugs in a wide range of doses. Moreover, apart from IMI, chronic treatment with all these neuroleptics was without any effect. The duration of immobility was reduced by CLZ, as it was for IMI. The data obtained for CLZ and IMI confirm previous results [3, 5, 7].

It is generally assumed that various antidepressant drugs reduce the duration of immobility in this test by activating noradrenergic and/or dopaminergic mechanisms in the rat brain [2, 6, 17]. On the other hand, it is known that neuroleptics block dopaminergic receptors and some of them are also antagonists of the noradrenergic receptors [1, 10, 14].

It is postulated that the main reason for the lack of effect of the above-mentioned neuroleptics in the swimming test even after chronic administration, is more due to their dopamine receptor blocking activity than their antagonism to the alpha-adrenoceptors. Some findings speak in favor of this supposition. First of all, phenoxybenzamine, the alpha-adrenoceptor blocking drug, in relatively high doses (4–16 mg/kg) has no effect on the immobility whereas haloperidol and pimozide, dopamine receptor blockers, in doses of 0.1 and 2.0 mg/kg respectively, increases the duration of the immobility [17]. Secondly, CLZ, which is a neuroleptic without apomorphine antagonism but with potent inhibitory action on the central alpha-adrenoceptors [14,21], significantly reduces the duration of the immobility (Table 1). Thirdly, locomotor and exploratory activities in the open field in rats chronically treated with LPZ, TRZ, c-CPX and t-CPX were not changed (Table 2), indicating that the treatment did not disturb the normal alpha-adrenergic transmission in the rat brain. Thus one may consider that the blockade of the central dopamine receptors by the neuroleptics masks their other activities which would normally cause significant effects in the forced swimming test.

The present results show that the immobility test is not a suitable pharmacological model for revealing antidepressant activities of certain neuroleptics, known to be useful in the treatment of certain forms of human depression.

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