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Effect of Changes in Swimming Area on Results of "Behavioral Despair Test"

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SUNAL, R., B. GÜMÜŞEL AND S. O. KAYAALP. *Effect of changes in swimming area on results of "behavioral despair test."* PHARMACOL BIOCHEM BEHAV **49**(4) 891-896, 1994. – Our previous observations have revealed that the total time spent in immobility and time to reach complete immobility (latency) vary with the diameter of the cylindric chamber where mice are forced to swim in the behavioral despair test. Therefore, we investigated the effect of changing the test conditions of the original Porsolt test. Mice were forced to swim for 15 min in chambers with 10 cm (original diameter of the Porsolt's forced swimming chamber), 20, 30, and 50 cm diameter in 20 cm deep water. Total time spent in spells of immobility during the observation period from third to sixth (inclusive) minutes and time to reach complete immobility were measured. In addition, a possible correlation between the rotatory locomotor activity of mice during swimming as assessed by the number of tours per minute and effect of antidepressant drugs on it was investigated. Total duration of spells of immobility was shorter and the latency was longer in tests carried out in chambers with 10 cm diameter. Increasing the diameter of the cylinders made it possible to distinguish the antidepressant drugs from caffeine, anticholinergics, and antihistaminics, which gave a false positive response in 10 cm diameter cylinders, but not in cylinders with larger diameters. Increasing the diameter of the chambers to 20 and 30 cm also allowed to study the selective effect of the antidepressants, namely, the rotatory locomotor activity during swimming. The extention of the test period to 15 min increased the reliability of the measurement of the time to reach complete immobility. These results indicate that the modifications described in this work increase the predictive power of the original Porsolt test used in screening the chemicals with a potential antidepressant property.

Behavioral despair Change in diameter Latency

FORCED swimming-induced immobility is an animal model of depression that is widely used to screen antidepressant activity. It was initially introduced by Porsolt et al., who observed that rats or mice, when forced to swim in a restricted space from which they cannot escape, cease to struggle and quickly maintain a characteristic immobile posture. And they correlated this despair behavior, expressed as immobility to the clinical state of mental depression (5-7).

The behavioral despair induced in this manner can be inhibited by prior administration of antidepressants as well as by electroconvulsive shock (ECS) and deprivation of REM sleep, which are also effective in relieving human depression. However, the original method is not without biases, and also false-positive results are obtained with stimulants, anticholinergics, and antihistaminics (1-3).

To eliminate the subjectivity factor and to increase specifity, a water wheel attachment to the inner wall of the chamber was introduced by Nomura et al. (3). The number of rotations per minute of the wheel moved by test animal was reported to be inversely related to the immobility score of the animal. Events like escape from a provided rope, swimming under water or along the side of the tank, and passive sinking have all been proposed as indices of depression (2,7,8). Recently, it has been reported that dimensions of the test apparatus affect immobility during forced swimming test and whether or not the original size of the tank is optimal for the emotional despair is still a question to be answered (1,2,10).

During our preliminary studies we observed that in the original Porsolt test, the animal becomes immobile by touching the sides of the chamber with its forepaws and the bottom of the chamber with its tail. We, therefore, attempted to improve the antidepressant action predictivity of the test by: a) investigating the effect of changes in diameter of swimming chambers on total time spent in immobility spells, b) assessing the time elapsed to reach permanent immobility (latency) because our previous observations revealed that following the

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initial immobility that occurred during the first 6 min of the test, the animal became active again, this time for a longer period, c) evaluating the rotatory swimming in chambers 20 or 30 cm diameter as a new parameter to assess antidepressant activity.

METHOD

Animals

Naive male and female local bred albino mice (Charles River) 8–10 weeks old (20–24 g) were used. One week prior to testing, mice were housed in groups of six in a ventilated room at 25°C with free access to food and water. Mice were handled gently daily to eliminate stress due to handling on the test day. Six mice were used for each test and control group.

General Procedure

In the original Porsolt test (4,5) the antidepressant drugs were administered by single injection 1 h prior to testing. We also used the same drug administration protocol. However, initial experiments revealed that pretest is not necessary. Naive mice were forced to swim inside vertical Plexiglas cylinders (height: 30 cm, diameter: 10, 20, 30, and 50 cm) containing 20 cm deep water at 25°C. They were observed for 15 min. Total duration of immobility periods from the third to sixth (inclusive) minutes, time to reach complete immobility (latencies), and the tours per minute during the 15-min test period were measured.

Treatment

The drugs and doses tested are as follows: chlorimipramine (tricyclic antidepressant) 10 and 20 mg/kg, maprotyline (nontyricyclic antidepressant) 7.5 and 15 mg/kg, tranylcypromine (MAO inhibitor) 10 and 20 mg/kg, reserpine 1 mg/kg, atropine (anticholinergic) 1 and 10 mg/kg, caffeine (CNS stimulant) 7.5 and 15 mg/kg, diazepam (anxiolytic) 5 and 10 mg/kg, haloperidol (neuroleptic) 0.05 and 0.1 mg/kg, chlorphenoxamine HCl (antihistaminic) 15 and 30 mg/kg. The drugs were either dissolved in distilled water or dispersed in a suspension of Tween 80 (2% w/v in 0.9% NaCl). Control animals received vehicle only. Drugs were injected IP in a constant volume of 0.1 ml/kg 1 h before the test except reserpine, which was injected 4 h prior to testing (5).

Electroconvulsive Shock (ECS)

Supramaximal ECS (30 mA, 50 Hz, 1 s) was generated using a Grass Constant Current Unit 1 A and delivered via eye electrodes. Control mice had the same electrodes placed in a similar manner but without ECS.

Statistical Analysis

The same statistical analysis method of Porsolt test was used (5–7). Statistical differences between groups were assessed by using Dunnett's test (two tailed). The level of significance was chosen as $p < 0.05$.

RESULTS

Preliminary experiments revealed that: a) there was no statistically significant difference between groups that received pretesting 24 h prior to test and test groups ($p > 0.005$); b) in the pretesting that was employed 1 h prior to test, the time between pretesting and test was very short; thus, we observed a decrease in all the results. To confirm that this decrease is caused from the tiredness of the mice, rotarod activity test was performed. Because the rotarod activities of animals 1 h after pretest also decreased, we did not use pretest in our experiments.

Effect of Change in Diameter on Latency

Latencies in 30 and 50 cm chambers as measured by time to reach permanent immobility were longer than in 10 cm cylinders. The antidepressant drugs increased the latency in 20, 30, and 50 cm diameter chambers ($p < 0.05$) (Table 1).

Effect of Drugs Other Than Antidepressants and ECS on Latency

ECS alone enhanced the latencies in all chambers (Table 1). Atropine 10 mg/kg, caffeine 15 mg/kg, and chlorphenoxamine 30 mg/kg IP increased latencies only in 10 cm diameter chamber. However, in 20, 30, and 50 cm diameter chambers, none of the nonantidepressant drugs caused a change (Table 2).

Total Duration of Immobility Spells During the Third to Sixth Minutes

The total duration of immobility in tests carried out in 10 cm diameter chamber was significantly lower than in the 20, 30, and 50 cm diameter chambers ($p < 0.05$). Both antidepressant and the nonantidepressant drugs, i.e., 1 and 10 mg/kg atropine, 15 mg/kg caffeine, and 30 mg/kg chlorphenoxamine, reduced the total time spent in immobility in 10 cm diameter chamber. However, in 20, 30, and 50 cm diameter chambers an inhibition of immobility was only observed with the antidepressants and ECS but not with atropine and chlorphenoxamine (Table 3).

Effect of Antidepressants on Rotatory Swimming Activity of Mice

Because, in the preliminary experiments, it was observed that 10 cm diameter chambers did not have enough space for animals to swim around, and 50 cm chambers were too large and the mice preferred to swim in the middle of the cylinder, 10 and 50 cm chambers were omitted in this part of the experiment. All antidepressant drugs tested at all dose levels and also ECS increased the rotatory number of tours per minute or cumulative number of tours during the 15-min observation period. So, the nonantidepressant drugs, atropine, cafeine, chlorphenoxamine, diazepam, and haloperidol did not affect either the number of tours per minute or the cumulative number of tours per 15 min (Table 4).

Discussion

Although the Porsolt forced swimming induced behavioral despair model is capable of predicting a variety of potential antidepressants, it is not devoid of biases. It gives false positive results with anticholinergics, antihistaminics, and CNS stimulants. And furthermore, recently questions have been raised on whether or not the duration of immobility measured is a state of despair and the relevance of this despair to depression (1,10).

We have observed that increasing the diameter of the cylinder reduced the duration of immobility during third, fourth, fifth, and sixth minutes of the test period in control groups. Our results revealed that in 10 cm cylinders mice, soon after

TABLE 1

EFFECT OF CHANGE IN DIAMETER ON LATENCY DURING THE 15-MIN TEST PERIOD

	Diameter (cm)										
	10		20			30			50		
Drugs	Latency (s)	Change from Control (%)	Latency (s)	Change from Control (%)	Change from 10 cm (%)	Latency (s)	Change from Control (%)	Change from 10 cm (%)	Latency (s)	Change from Control (%)	Change from 10 cm (%)
Control	374 ± 33.56		499.8 ± 85.84		33.49	570 ± 37.28		52.24†	619 ± 47.79		65.33†
Chlomipramine 10 mg/kg	416.3 ± 23.24	11.19	555 ± 66.04	11.04	33.36	613 ± 30.29	7.54	47.24†	835 ± 36.06	34.89*	100.57†
Chlomipramine 20 mg/kg	527 ± 44.29	40.75	668 ± 29.02	33.65	26.75	715 ± 33.67	25.43	35.67†	900 ± 0	45.39*	70.78†
Maprotyline 7.5 mg/kg	490 ± 38.26	30.87	600 ± 47.56	20.04	22.44	780 ± 25.29	36.84*	59.15†	850 ± 29.49	37.31*	73.46†
Maprotyline 15 mg/kg	534 ± 97.22	42.63	791 ± 45.8	58.26*	48.12†	823 ± 23.83	44.38*	54.12†	900 ± 0	45.39*	68.54†
Tranylcypromine 10 mg/kg	588 ± 42.56	30.34	781 ± 30.07	56.2*	60.04†	841 ± 43.15	47.54*	72.33†	848 ± 27.1	36.99*	73.77†
Tranylcypromine 20 mg/kg	559 ± 47.76	49.3*	846 ± 31.74	69.2*	51.34†	831 ± 21.74	45.78*	48.66†	900 ± 0	45.39*	61.00†
ECS	564 ± 38.45	50.64*	752 ± 54.19	50.46*	33.33	879 ± 46.04	54.21*	57.24†	875 ± 22.51	41.35*	55.14†

Values represent the means ± SEM ($n = 6$).

*Significant compared to control (Dunnet's test; $p < 0.05$).

†Significant compared to 10 cm (Dunnet's test; $p < 0.05$).

TABLE 2

EFFECT OF CHANCE IN DIAMETER ON LATENCY DURING THE 15-MIN TEST PERIOD

	Diameter (cm)										
	10		20			30			50		
Drugs	Latency (s)	Change from Control (%)	Latency (s)	Change from Control (%)	Change from 10 cm (%)	Latency (s)	Change from Control (%)	Change from 10 cm (%)	Latency (s)	Change from Control (%)	Change from 10 cm (%)
Control	374.4 ± 33.56		499.8 ± 85.84		33.49	570 ± 37.28		52.24	619 ± 47.79		65.33
Rezerpine 5 mg/kg	382.5 ± 26.64	2.16	442.5 ± 28.85	−11.46	15.68	545 ± 24.21	−4.38	42.48	507.6 ± 56.61	−17.99	32.7
Rezerpine 10mg/kg	315 ± 17.32	−15.86	390 ± 22.7	−21.97	23.8	660 ± 29.71	15.78	109.52	810 ± 18.17	30.85	157.14
Atropine 1 mg/kg	435 ± 19.13	16.18	462.5 ± 37.02	−7.46	6.32	492.5 ± 16.6	−13.59	13.21	515 ± 35.4	−16.8	18.39
Atropine 10 mg/kg	557.5 ± 23.05	48.9*	555 ± 31.02	11.04	−0.44	592.5 ± 29.5	3.94	6.27	650 ± 54.19	5.3	16.59
Caffeine 7.5 mg/kg	410 ± 28.6	9.5	490 ± 54.03	−1.96	19.51	492 ± 21.2	−13.68	20	622.5 ± 47.6	0.56	51.82
Caffeine 15 mg/kg	560 ± 42.04	49.57*	547.5 ± 41.69	9.54	−2.23	587.4 ± 30.71	3.05	4.89	690 ± 14.79	11.47	523
Diazepame 5 mg/kg	355 ± 25.16	−5.18	473.2 ± 15.56	−5.32	33.29	503 ± 38.6	−11.75	41.69	614 ± 28.74	−0.81	72.95
Diazepame 10 mg/kg	370 ± 29.4	−1.17	455 ± 37.16	−8.96	22.97	572 ± 48.8	0.35	54.59	579 ± 33.45	−6.46	56.48
Haloperidol 0.05 mg/kg	348 ± 35.7	−7.05	439 ± 29.11	−12.16	26.15	543 ± 67.5	−4.73	56.03	630 ± 45.63	1.77	81.03
Haloperidol 0.1 mg/kg	342 ± 41.19	−8.05	462 ± 49.28	−7.56	35.08	568 ± 17.83	−0.35	66.08	624 ± 21.09	0.85	82.45
Chlorphenoxamine 15 mg/kg	417 ± 20.03	11.37	528 ± 16.7	5.64	26.61	595 ± 24.62	4.38	42.68	673.2 ± 39.5	8.75	61.43
Chlorphenoxamine 30 mg/kg	553 ± 18.34	47.70*	576 ± 40.8	15.24	4.15	610 ± 33.73	7.01	10.48	711 ± 49.12	14.86	28.57

Values represent the means ± SEM ($n = 6$).

*Significant compared to control (Dunnet's test, $p < 0.05$).

TABLE 3

EFFECT OF CHANGE IN DIAMETER ON IMMOBILITY TIMES DURING 3rd, 4th, 5th AND 6th MINUTES

	Diameter (cm)							
	10		20		30		50	
Drugs	Duration of Immobility (s)	Change from Control (%)	Duration of Immobolity (s)	Change from Control (%)	Duration of Immobility (s)	Change from Control (%)	Duration of Immobility (s)	Change from Control (%)
Control	135.25 ± 12.95		52.5 ± 9.10		40.3 ± 13.26		29 ± 5.59	
Chlomipramine 10 mg/kg	61.86 ± 5.77	−54.26*	18.07 ± 3.95	−65.58*	26.27 ± 5.06	−34.8*	16.85 ± 3.27	−41.9*
Chlomipramine 20 mg/kg	38.28 ± 1.98	−71.6*	11.75 ± 1.55	−77.67*	11.81 ± 2.16	−70.7*	9.19 ± 1.33	−68.3*
Maprotyline 7.5 mg/kg	56.66 ± 3.5	−58.59*	15.68 ± 2.89	−70.12*	16.47 ± 3.76	−59.14*	13.9 ± 2.25	−52.06*
Maprotyline 15 mg/kg	27.23 ± 3.67	−79.86*	8.3 ± 2.6	−84.18*	9.3 ± 3.12	−76.92*	9.4 ± 1.34	−67.6*
Tranylcypromine 10 mg/kg	49.71 ± 2.11	−63.24*	17.6 ± 3.15	−66.4*	21.76 ± 2.9	−16*	10.87 ± 2.23	−62.48*
Tranylcypromine 20 mg/kg	30.53 ± 2.95	−77.43*	6.434 ± 1.19	−87.75*	8.27 ± 2.35	−79.46*	5.03 ± 1.39	−82.65*
ECS	67.4 ± 8.62	−50.16*	17.62 ± 5.55	−66.43*	15.38 ± 6.71	−61.83*	11.05 ± 4.18	−61.89*
Rezerpine 5mg/kg	158.4 ± 18.35	17.12	66.31 ± 12.1	26.3	52 ± 11.2	29.03	54 ± 7.05	87.9
Rezerpine 10 mg/kg	181.5 ± 16.64	34.2	88.49 ± 11.16	68.5	59.2 ± 8.4	46.89	56.3 ± 6.4	94.13
Atropine 1 mg/kg	93.45 ± 17.09	−30.9*	76.5 ± 4.95	45.7	44.5 ± 8.5	10.4	24.5 ± 3.9	−15.5
Atropine 10 mg/kg	67.42 ± 5.17	−50.15*	38.13 ± 11.2	−27.4	37.2 ± 4.2	−7.69	38.1 ± 6.4	31.38
Caffeine 7.5 mg/kg	109 ± 12.73	−19.4	54.5 ± 9.4	3.8	76.21 ± 17.54	89.1	49.15 ± 9.98	69.5
Caffeine 15 mg/kg	74.65 ± 4.25	−44.8*	48.32 ± 7.13	−7.96	64.5 ± 13.5	60.04	42.4 ± 9.55	46.2
Diazepame 5 mg/kg	149.2 ± 23.69	10.31	59.12 ± 4.48	12.6	42.13 ± 9.51	4.54	32.3 ± 4.71	11.3
Diazepame 10 mg/kg	138.51 ± 17.63	2.4	55.7 ± 9.81	6.09	49.5 ± 7.13	22.8	27.25 ± 8.5	−6.03
Haloperidol 0.05 mg/kg	123.48 ± 14.8	−8.7	50.5 ± 13.01	−3.8	51.35 ± 4.53	27.42	27.4 ± 4.3	−5.5
Haloperidol 0.1 mg/kg	131.25 ± 19.4	−2.96	53.07 ± 12.6	1.08	48.5 ± 6.3	20.34	35.25 ± 2.72	21.3
Chlorphenoxamine 15 mg/kg	105.13 ± 1046	−22.27	48.56 ± 12.05	−7.5	37.5 ± 6.04	−6.92	22.1 ± 4.15	−23.8
Chlorphenoxamine 30 mg/kg	89.71 ± 6.12	−33.67*	38.72 ± 8.7	−26.2	29.32 ± 5.18	−27.24	18.57 ± 5.8	−35.9

Values represent the means ± SEM ($n = 6$).
*Significant compared to control (Dunnet's test; $p < 0.05$).

immersion into water, learn to stay afloat by touching their fore and hind paws to the sides and by their tails to the bottom of the cylinder and thus exert less effort.

However, with an increase in the diameter of the cylinder, mice loose their chance to touch the sides and the bottom of the cylinder and, thus, are forced to swim. We, therefore, observed significant inhibition of duration of immobilities even in control groups (Table 3). Duration of immobility in 30 and 50 cm diameter cylinders were significantly lower than 20 cm cylinders, and duration of immobility in 30 cm was significantly lower 50 cm cylinders.

Because increase in diameter decreases duration of immobility, mice were still active after the sixth minute of the test. So, in 10 cm cylinders Porsolt et al. have reported that immobility begins at the third minute and a complete immobility is reached after the seventh minute which lasts during the following 8 min. Therefore, the parameter we used to assess behavioral despair has been the duration of immobility within the third to sixth minutes expressed as latency.

Moreover, our investigation of the time the mice needed to reach complete immobility (recorded as latency) has revealed that 15 min are needed for the mice to loose all their hopes of escape and stay afloat, and only antidepressant drugs increase the latencies compared to controls.

With the increase in diameter, a change in the posture of the animals was also observed. Mice withdrew their fore and hind limbs to their abdomens and floated in this position and their posture did not change either during removal from water or after. So, in 10 cm cylinders, an attempt of removing them from the water tank induces mobility. Control groups, upon removal from water, had pitozis and hypothermia. The pitozis continued for a further 2.5 h.

These results suggest that the behavioral despair observed in 10 cm cylinders is different from the behavioral despair obtained in 20, 30, and 50 cm cylinders, and that the immobility achieved in 10 cm cylinders is rather a learned stillness than a despair. Our results also indicate that the optimum diameter for inducing behavioral despair is 30 cm.

Psychomotor retardation is one of the main symptoms of depression. Nomura et al. (4) reported that all the antidepres-

TABLE 4

EFFECT OF CHANGE DIAMETER ON TOURS/MIN DURING THE 15-MIN TEST PERIOD

	Diameter (cm)				
	20		30		
Drugs	Tours/15 min	Change from Control (%)	Tours/15 min	Change from Control (%)	Change from 20 cm (%)
Control	26.6 ± 2.49		30.2 ± 1.47		13.53
Chlomipramine 10 mg/kg	54.05 ± 2.93	103.19*	63.8 ± 1.92	111.3*	18.03
Chlomipramine 20 mg/kg	64 ± 1.95	140.6*	53.6 ± 5.01	77.48*	−16.25
Maprotyline 7.5 mg/kg	54.6 ± 1.76	105.26*	49.73 ± 3.57	64.66*	−8.91
Maprotyline 15 mg/kg	58 ± 2.93	118.04*	60.6 ± 3.43	100.67*	4.48
Tranylcypromine 10 mg/kg	56.4 ± 5.5	112.03*	79.3 ± 3.8	162.58*	40.6
Tranylcypromine 20 mg/kg	82 ± 5.45	208.2*	79.7 ± 4.64	163.9*	−2.8
ECS	48.3 ± 6.13	81.57*	45.6 ± 3.45	50.99*	−5.59
Rezerpine 5 mg/kg	21.2 ± 2.53	−20.3	27.4 ± 2.15	−10.16	29.24
Rezerpine 10 mg/kg	18.7 ± 3.62	−29.69	39.5 ± 3.01	30.79	111.22
Atropine 1 mg/kg	25.6 ± 2.83	−3.76	28.75 ± 5.56	−4.8	12.3
Atropine 10 mg/kg	29.45 ± 3.55	10.71	34.35 ± 3.032	13.74	16.64
Caffeine 7.5 mg/kg	27.3 ± 4.31	2.63	32.03 ± 4.1	6.05	17.32
Caffeine 15 mg/kg	30.5 ± 5.4	14.66	36.5 ± 3.8	20.86	19.67
Diazepame 5 mg/kg	23 ± 3.95	−13.53	28.6 ± 5.54	−5.29	24.34
Diazepame 10 mg/kg	24.75 ± 5.18	−7.89	30.1 ± 2.95	−0.33	21.6
Haloperidol 0.05 mg/kg	24.6 ± 4.01	−7.5	25.2 ± 5.53	−16.55	2.43
Haloperidol 0.1 mg/kg	25.3 ± 6.08	−4.88	28.9 ± 3.12	−4.3	14.22
Chlorphenoxamine 15 mg/kg	29.2 ± 2.8	9.77	32.5 ± 6.15	7.61	11.3
Chlorphenoxamine 30 mg/kg	32.4 ± 3.14	21.8	35.85 ± 2.7	18.67	10.64

Values represent the means ± SEM ($r = 6$).
*Significant compared to control (Dunnet's test; $p < 0.05$).

sants they tested increased the number of rotations in a water wheel they attached to the swimming tank. Instead, we assessed the rotatory swimming of mice by counting tours/minute and tours/15 min. For this purpose 20 and 30 cm diameter cylinders were used. In both seizes, tours/min decreased with time in control animals. In animals treated with antidepressants, both tours/min and tours/15 min increased significantly, suggesting this parameter as a good criteria for determining antidepressant activity.

The most striking result obtained by increasing the diameter of the cylinder was that the anticholinergics, antihistaminics, and CNS stimulants did not give false-positive results either when latency and duration of immobility or tours per minute was used as criteria.

We, therefore, concluded that, increase in the diameter of the cylinder facilitates: a) discrimination of antidepressant activity from CNS stimulation, anticholinergic, or antihistaminic activities, b) recording of latencies that is a more precise method to assess antidepressant activity.

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