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Behavioral Responses of High and Low Active Male Rats to the Chronic Ingestion of Desipramine[1]

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ECHANDÍA, E. L. R., S. T. BROITMAN AND M. R. FÓSCOLO. *Behavioral responses of high and low active male rats to the chronic ingestion of desipramine.* PHARMACOL BIOCHEM BEHAV 22(6) 917–920, 1985.—Male rats arbitrarily selected for high and low motor activity (HA and LA-rats) were submitted to the chronic ingestion (30 days) of desipramine (DSP) in doses of about 1.5, 3 and 6 mg/kg/24 hr. Their motor activity was assessed in an animal activity monitor providing a measure of total horizontal movements and vertical movements and in a hole-board providing a measure of locomotion, head-dipping and grooming. There were significant differences between HA and LA-rats in their behavioral response to DSP treatment. At the doses used DSP did not affect horizontal and vertical movements and hole-board locomotion or exploration in HA-rats (Experiment 1). In LA-rats, however (Experiment 2), these motor activities were significantly stimulated by DSP. Such effect was dose dependent; 1.5 mg/kg/24 hr was ineffective while 6 mg/kg/24 hr produced a clear cut reversion of hypoactivity. It is speculated that DSP treatment increased resistance of LA-rats to the mild stress caused by testing.

Desipramine Hyperactivity Hypoactivity Rats

INTERINDIVIDUAL variability in response to some psychoactive agents have been long detected in both human patients and laboratory animals. Until recently, however, little attention was payed to the relative importance of this phenomenon. It may reflect the neurochemical adaptive changes of the individual subjects in response to psychoactive drugs.

Correlations between spontaneous motor activity and forebrain monoamine function have been reported. Rats screened by high activity would metabolize forebrain serotonin (5-HT) at a greater rate than rats selected by low activity. The opposite was found for the metabolism of brain noradrenaline (NA) suggesting that low active rats have a more functional NA system [11,13]. It was considered, therefore, that an analysis of behavioral responses of high active and low active rats to chronic administration of tricyclic antidepressants might be of interest.

In this work male rats showing maximal and minimal scores of locomotor activity were arbitrarily selected for the experiments. These high active (HA) and low active (LA) rats were submitted to chronic ingestion of the secondary amine tricyclic, desipramine (DSP). When given chronically this tricyclic causes a preferential down regulation of the NA-receptor-coupled adenylate cyclase system in the brain [17]. The data presented indicate that there are strong relationships between baseline activity of rats and the locomotor and exploratory responses to chronic DSP treatment. This treatment did not affect hyperactivity but produced a dose dependent reversion of hypoactivity.

METHOD

Subjects

Male rats from a Holtzman derived colony bred at our laboratory were used. These were allocated in groups of 5 in stainless steel cages (40×27×20 cm) and maintained at 23±1°C with 14 hr light-10 hr dark cycle, with lights on at 6:00 hr. Food pellets and water were available ad lib. The rats were undisturbed except for weekly cleaning of their cages or food and water supply.

Baseline Motor Activity of Rats

At 90–100 days of age rats were tested for individual differences in baseline motor activity in an animal activity monitor followed by a holeboard test.

Animal Activity Monitor Test

The spontaneous motor activity was monitored in a 5 min test during which each rat was placed singly in the 45×45×20.5 cm transparent plastic cage of a Columbus animal activity monitor (Opto-Varimex III, Columbus Instruments Internat, CO) provided with horizontal and vertical infrared screen sensors. The following motor activities

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TABLE 1

BASELINE SCORES OF RATS SELECTED BY HIGH AND LOW LEVELS OF MOTOR ACTIVITY AT 90–100 DAYS OF AGE (5-MIN TRIALS)

	HA-rats	LA-rats
Animal activity monitor test		
Total horizontal movements (counts)	3524.0 ± 155.94	1894.7 ± 141.98
Vertical movements (counts)	61.1 ± 3.64	24.4 ± 2.33
Defecation (N°)	1.5 ± 0.70	2.6 ± 0.51
Hole-board test		
Locomotion (N°)	93.7 ± 4.04	59.0 ± 7.47
Head-dipping (N°)	19.8 ± 3.44	8.0 ± 1.36
Head-dipping (sec)	24.5 ± 3.37	12.9 ± 2.43
Grooming (N°)	6.2 ± 0.87	8.7 ± 2.32
Grooming (sec)	12.1 ± 1.48	16.0 ± 2.41
Defecation (N°)	1.0 ± 0.58	3.5 ± 0.91

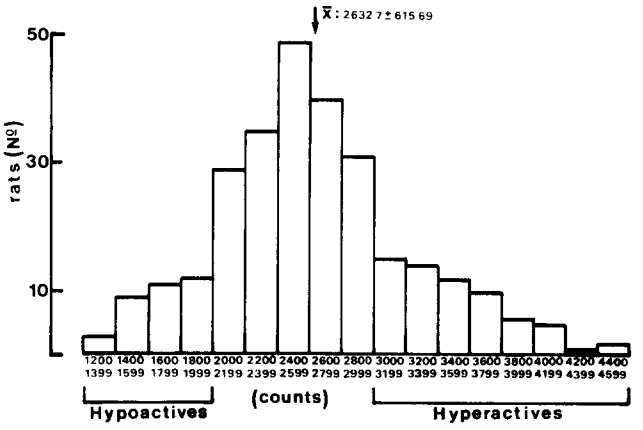

FIG. 1. Histogram of frequencies of baseline total horizontal movements (counts/5 min) of the rats tested for high and low levels of motor activity. x̄ = mean±standard deviation.

were recorded via the electrical counters: (a) Total horizontal movements (ambulatory and non ambulatory movements) and (b) vertical movements (rearing). At the end of the trial the rat was removed, the incidence of defecation was scored and the cage was wiped. All trials were performed between 11:30 and 13:30 hr. After testing rats were maintained undisturbed for 48 hr, then submitted to a hole board test.

Hole-Board Test

The arena was a square surface painted black (1.0×1.0 m) with 35 cm high walls. The plastic floor was marked off in 20×20 cm squares with holes, each 2.0 cm in diameter, spaced 20 cm apart from one another. The field was placed 20 cm above the floor of the room and a single 40 W lamp was suspended over the center of the arena 2.8 m from the floor. The rats were placed singly in the center of the field for a 5 min trial and scores of locomotion (number of squares entered completely by each rat), exploration (frequency and time spent head dipping) and grooming (frequency and time spent washing, scratching and licking) were obtained by direct observation.

Selection of HA and LA Rats

Testing was completed on 283 rats from which HA and LA individuals were arbitrarily selected. HA-rats were the ones displaying total horizontal movements above 3000 counts and hole-board locomotion above 90. LA-rats were the ones showing total horizontal movements below 2000 counts and hole-board locomotion below 60. A majority of rats gave scores intermediate between HA and LA-rats and were discarded. The baseline scores of HA and LA-groups are tabulated in Table 1. Figure 1 is a frequency histogram of total horizontal movements of the rats tested for baseline activity.

Experiment 1

The HA-rats assigned to Experiment 1 were randomly distributed in 4 subgroups (each n=15). Analysis of scores of baseline motor activity showed that differences between groups did not reach statistical significance (results not shown). The 3 experimental subgroups were provided with water containing 12.5, 25 and 60 mg/kg DSP respectively. The subgroup of controls received tap water devoid of drug. The amount of drug ingestion (mean±SEM) of the experimental subgroups was 1.5±0.32, 3.0±0.29 and 5.9±0.41 mg/kg/24 hr. These values were calculated from the mean amount of water intake/24 hr cage. After 30 days of DSP ingestion rats were resubmitted to an animal activity monitor test and continued consuming DSP until the hole-board test was completed. The procedure was similar to that used for obtaining baseline scores at 90–100 days of age.

Experiment 2

The LA-rats assigned to Experiment 2 were also distributed into 4 subgroups (each n=10). The experimental subgroups were provided with water containing DSP in amounts similar to those reported for Experiment 1. The amounts of drug ingestion (mean±SEM) of these subgroups were 1.4±0.21, 3.1±0.29 and 6.2±0.38 mg/kg/24 hr. The LA-controls received water devoid of DSP. Testing started after 30 days of drug ingestion and was performed as shown for Experiment 1.

Comparison of data at Table 1 and control columns at Figs. 2 and 3 and data presented in the Results section provides evidence for stability of responses of HA and LA-rats to test (90–100 days of age)- retest (120–130 days of age) situations.

Statistics

Data were analyzed by the one way analysis of variance (ANOVA) and the Duncan's multiple range test. Data are presented as means±SEM. A level of probability of less than 0.05 was considered significant.

RESULTS

Experiment 1. Effect of DSP Treatment in HA-Rats

Animal activity monitor test. In this test, differences in motor responses between HA-DSP groups and HA-controls

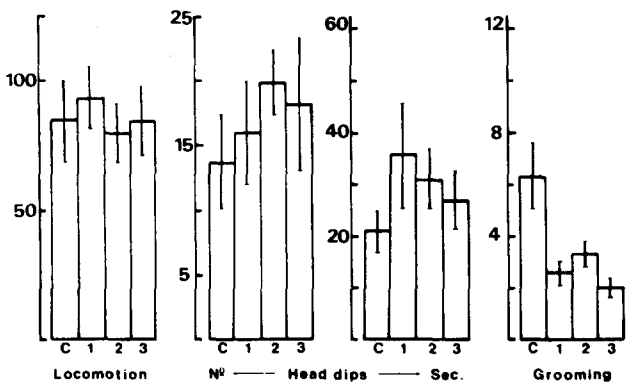

FIG. 2. Hole-board test. Mean scores±SEM of HA-rats. C: HA-controls. 1: HA-DSP 1.5 mg/kg/24 hr. 2: HA-DSP 3 mg/kg/24 hr. 3: HA-DSP 6 mg/kg/24 hr.

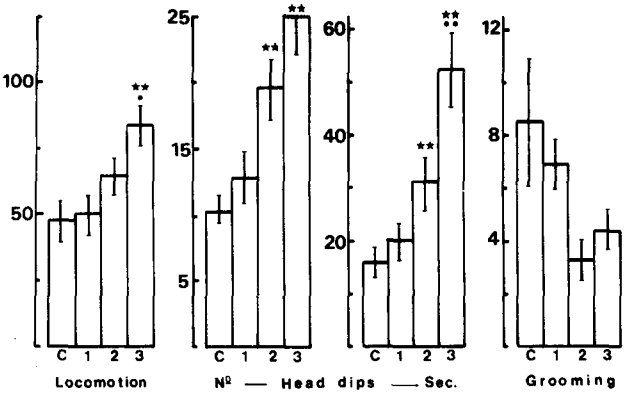

FIG. 3. Hole-board test. Mean scores±SEM of LA-rats. C: LA-controls. 1: LA-DSP 1.5 mg/kg/24 hr. 2: LA-DSP 3 mg/kg/24 hr. 3: LA-DSP 6 mg/kg/24 hr. Large stars: $p<0.01$ vs. LA-controls. Small stars: $*p<0.05$ and $**p<0.01$ for LA-CIM 6 mg/kg vs. LA-CIM 3 mg/kg (Duncan's multiple range test).

were not found. The scores of total horizontal movements (HA-controls: 3028.0±290.15; HA-DSP 1.5 mg/kg: 3153.6±135.31; HA-DSP 3 mg/kg: 3328.0±115.29; HA-DSP 6 mg/kg: 3272.6±263.57), vertical movements (HA-controls: 42.0±5.96; HA-DSP 1.5 mg/kg: 59.0±14.65; HA-DSP 3 mg/kg: 41.9±3.69; HA-DSP 6 mg/kg: 58.0±13.44) and defecation (results not shown) were similar for all groups.

Hole-board test. Consistently, the DSP treatment had no effects on hole-board locomotion and exploration (frequency and time spent head dipping) of HA-rats (Fig. 2). This was the case also for the incidence of defecation (results not shown). All groups of HA-DSP rats showed less frequency and time spent grooming than HA-controls but differences did not reach significance (Fig. 2).

Experiment 2

Animal activity monitor test. Significant between-groups differences in the scores of total horizontal movements were found (LA-controls: 1842.1±114.1; LA-DSP 1.5 mg/kg: 1837.5±131.33; LA-DSP 3 mg/kg: 1894.7±141.98; LA-DSP 6 mg/kg: 2222.2±61.82; $F(2,26)=9.79$, $p<0.005$). The Duncan's test revealed that such differences were due to the LA-DSP group treated with 6 mg/kg DSP ($p<0.01$). In this group the scores of vertical movements tended to be higher than controls (LA-controls: 23.6±3.73; LA-DSP 6 mg/kg: 30.2±5.11) but differences were not significant. As to the incidence of defecation the scores were statistically similar in LA-DSP groups and LA-controls (results not shown).

Hole-board test. Figure 3 illustrates the scores of hole-board locomotion of LA-groups. Significant between-groups differences in these scores were found, $F(2,23)=9.74$, $p<0.05$. The Duncan's test showed that such differences were due to the higher scores of the LA-group treated with DSP in doses of 6 mg/kg/24 hr (LA-controls vs. LA-DSP 6 mg/kg: $p<0.01$). Hole-board locomotion was not affected by DSP in doses of 1.5 mg/kg/24 hr but tended to increase in the group of LA-rats treated with 3 mg/kg/24 hr (Fig. 3).

Chronic DSP treatment increased hole-board exploration of LA-rats in a dose dependent manner (Fig. 3). Between-groups differences in the scores of frequency of head dips, $F(2,23)=4.81$, $p<0.02$, and time spent head dipping, $F(2,23)=21.17$, $p<0.005$, were observed. The Duncan's test revealed the DSP in doses of 1.5 mg/kg/24 hr was ineffective on hole-board exploration but both frequency and time spent head dipping increased significantly in the group treated with 3 mg/kg/24 hr (LA-controls vs. LA-DSP 3 mg/kg: $p<0.01$). This effect was higher in the group treated with 6 mg/kg 24 hr (LA-DSP 3 mg/kg vs. LA-DSP 6 mg/kg: $p<0.05$ for frequency of head dips and $p<0.01$ for time spent head dipping). Between-groups differences in the scores of frequency and time spent grooming were not found though this activity tended to decrease in the LA-groups treated with 3 and 6 mg/kg/24 hr DSP (FIG. 3). The incidence of defecation was similar for all groups of LA-rats (results not shown).

Figures 2 and 3 show that the scores of hole-board activities of the LA-group treated with 6 mg/kg/24 hr DSP were similar or even higher than the scores of HA-controls. When scores of locomotion and frequency of head dips of LA-DSP 6 mg/kg were compared to those of the HA-groups statistical differences were not found. As to the time spent head dipping, the scores of LA-DSP 6 mg/kg were higher than the scores of the HA-controls (Duncan test, $p<0.01$).

DISCUSSION

The present study provides evidence that there are strong relationships between spontaneous motor activity and responsiveness of some behaviors to the chronic treatment with a secondary amine tricyclic in rats. At the doses used chronic DSP did not affect total motor activity (total horizontal movements as well as vertical movements) and hole-board locomotion or exploration in HA-rats (Experiment 1). Interesting, in LA-rats (Experiment 2) these activities were clearly stimulated by DSP. The treatment induced a clear cut reversion of hypoactivity. Such effect was dose dependent; 1.5 mg/kg/24 hr was ineffective while 6 mg/kg/24 hr produced the maximal effects. Grooming activity was slightly depressed by DSP treatment in both HA and LA-rats but this effect did not reach significance and will not be treated in this discussion.

It is known that chronic antidepressant therapy produces no obvious effects on performance in normal human subjects; the treatment may improve performance of depressed

patients only. It is remarkable, therefore, that LA-rats were the ones sensitive to chronic DSP treatment. Certainly, hypoactivity in rats cannot be adscribed to any type of human depression. It may be speculated, however, that LA-rats are more sensitive than HA-rats to the mild stress of handling and novelty caused by testing. It was suggested previously that LA-rats would develop higher levels of fear than HA-rats [11]. On the other hand, the LA-rats selected for the present experiments showed higher baseline scores of defecation than HA-rats in both tests situations used (see Table 1). This evidence suggests that LA-rats may have a poorer adaptation to stress, which is apparently the case also for depressed patients (see [14] for review).

DSP has been reported to increase the resistance of rats to the behavioral deficit and corticosteroid response caused by foot shock and other stressors [5,12]. There is growing evidence that chronic antidepressant therapy induces subsensitivity to NA and 5-HT in the brain [4, 6, 10, 16]. The therapy would mimic therefore some of the adaptive neurochemical changes that normally occur during adaptation to stress (see [14] for review). It might be speculated that DSP treatment did increase resistance of LA-rats to emotional stressors and consequently stimulated performance at testing.

Opposite to this interpretation, however, is the fact that the LA- groups submitted to DSP treatments showed similar scores of defecation than their untreated controls in both test situations. This result would apparently contradict the possibility of a fear-reducing effect of chronic DSP in LA-rats. It is known, however, that caution must be taken in considering defecation as reflecting emotionality when using psychodrugs. An analysis of the effect of the chronic antidepressant treatment in HA and LA-rats submitted to depression-producing manipulations may eventually offer further light on this problem.

Other interesting features for future research are (1) the relationships between spontaneous activity and brain monoamine function as well as (2) the synaptic adaptive changes occurring in HA and LA-rats in response to chronic antidepressant treatments. On the bases of experiments on forebrain amine turnover as well as on metabolic and behavioral responses to MPT and p-CPA it was suggested that HA-rats would have a more functional 5-HT system than LA-rats. The latter would have a more functional NA system [11,13]. This view, however, is conflictive with a number of studies showing that increased NA function causes hyperactivity [2, 7, 16] while stimulation of 5-HT function causes hypoactivity in rats [1, 6, 10]. Further work is required for a more complete understanding of this subject.

Identification of the monoamine systems responsable for the effects of DSP in HA and LA-rats was out of the scope of this study. DSP is not a drug acting selectively on a single monoamine system ([8] and see [9] for review) but there is evidence that when given chronically it causes a preferential down regulation of the NA function in the brain through the NA-receptor coupled adenylate cyclase system [3, 15, 17]. It might be speculated, therefore, that the NA system may be involved in the behavioral response of LA-rats to chronic DSP treatment.

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