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Altered Adult Behavior of Mice Following Postnatal Treatment with Haloperidol[1]

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DALLEMAGNE, G. AND B. WEISS. *Altered adult behavior of mice following postnatal treatment with haloperidol.* PHARMAC. BIOCHEM. BEHAV. **16**(5) 761–767, 1982.—Haloperidol (1 and 2 mg/kg) was administered SC daily to BALB/c and Swiss/Webster mice from postnatal days 4 through 21. No consistent statistically significant drug effects were detected on growth and reflex development. Spontaneous motor activity increased significantly in both sexes of the Swiss/Webster outbred strain, and in the BALB/c males. Performance on a fixed ratio schedule of reinforcement of both male and female haloperidol-exposed mice was not statistically different from control performance. Interpretation of such data must take into account the sensitivity of the testing devices, the effects of repeated testing of a single animal, and the suitability of traditional statistical methods in developmental pharmacology and toxicology.

Postnatal treatment Haloperidol Mice Preweaning developmental assessment Spontaneous activity Operant conditioning

PREGNANT and nursing women sometimes receive neuroleptic medication. The consequences for the fetus and neonate are unclear, but arouse concern because the developing brain may be vulnerable to toxic processes to which adults are resistant. Animal models serve a critical role in the evaluation of such risk [14].

Neuroleptics administered directly to newborn rats and mice can modify the behavior of these animals during adulthood. Chlorpromazine has been the most extensively studied of these drugs. Impaired acquisition of avoidance behavior [4] and decreased activity in an open field [10] have been observed. Other studies, however, have reported no effects [5, 11, 32]. Equivocal results have also been found after administration of reserpine [15, 33, 34] and haloperidol [3, 10, 31]. These discrepancies can be partially explained by age differences at the time the drug was administered and when the animals were tested. Treatment duration, testing procedure, and sex differences are other sources of variation. In most such studies, preweaning development was seldom evaluated systematically and behavior during adulthood was usually assessed only once with no more than one or two test procedures.

The present work was undertaken to evaluate the long-term effects of postnatal administration of haloperidol to neonatal mice. In a first experiment, BALB/c mice supplied by an inbred colony were subjects. In a second experiment, the study was replicated with mice of the outbred Swiss/Webster strain.

EXPERIMENT 1

METHOD

Subjects

Twenty-four BALB/c females, from the Inbred Mouse Unit of the University of Rochester Environmental Health Sciences Center, were maintained in a temperature-regulated room (21°C) on a 12-hr light: dark cycle. Food (Purina Rodent Laboratory Chow, #5001) and water were available at all times, except when otherwise specified. On the day of birth (day 1), the litters were counted and culled to 4 to 6 pups.

Before weaning, all pup manipulations were performed under an infrared lamp (approximately 38°C) to prevent a sharp fall of body temperature. At weaning, the offspring were sorted by sex, coded by ear punch, and housed by dose and sex in groups of 3 per cage. They were weighed subsequently at specific ages.

Drug Procedure

Haloperidol (Haldol, McNeil Laboratories) was provided as the lactate in 5 mg/ml ampules. It was diluted (5 or 10 times) to the required concentration with distilled water and stored under refrigeration. Fresh solutions were made every 2 or 3 days. Control animals received a comparable volume of fresh distilled water.

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Beginning on day 4, and daily until day 21, each pup was weighed and injected subcutaneously (0.25 ml Becton-Dickinson glass syringe with a 27-gauge needle) with 0, 1 or 2 mg/kg of haloperidol (8 litters per dose group). The total volume of injection was 10 ml/kg. To avert confusion, all offspring belonging to the same litter received the same drug treatment.

Behavioral Testing

Preweaning testing. Reflex assessment was performed, without blind coding, during the preweaning period either on the whole litter or on randomly chosen offspring when the entire litter could not be accomodated. It included:

(1) Simple righting reflex (day 6): The pup was placed in a supine position on a smooth surface. The time spent to return to a prone position was determined.

(2) Swimming test (day 9): A container (30 cm long, 19 cm large, 13 cm high) was filled with lukewarm water (approximatively 35°C). Each pup to be tested was dropped in the bath and observed for several seconds. The percentage of pups swimming straight was calculated.

(3) Grasping reflex (day 10): Each tested pup was placed on a 6 mm wire-mesh grid which was tipped over and gently shaken. The percentage of pups able to grasp the mesh was recorded.

(4) Eye opening: Once the eyes started to open, the percentage of pups per litter with eyes open was recorded daily.

Spontaneous activity testing. No more than one male and one female per litter, randomly selected, were tested in each test. Due to the limited number of subjects, the same animal was usually used more than once. Thirty-three out of the 95 mice were tested in three different apparatuses; 33 were used in two devices, and 29 in one. The testing apparatuses comprised:

(1) Activity cage (BRS/LVE, model PAC-001). It consisted of a large black cylinder, 45 cm in diameter and 38 cm high. The floor was adjusted 2 cm below 6 infared photobeams which were interrupted by horizontal movements of the mice. The number of beams interrupted by a group of 3 mice during a 5-minute period was recorded on two 4-digit counters. The mice were tested at 22 weeks of age.

(2) Circular alley [18]. The alley was bounded by 2 transparent Plexiglas cylinders (one 25 cm, the other 13 cm in diameter). Four infrared photobeams intersected the alley 2 cm from the floor. The apparatus was enclosed in a light-shielded wood cubicle. The number of beams interrupted by individual mice tested in the dark during a one-hour session was recorded on a counter and cumulative recorder. Six mice per group and sex were tested at 24 weeks of age.

(3) Operant chamber (Lehigh Valley model 143-02). These chambers were constructed of two Plexiglas and two aluminum panels, a grid floor and Plexiglas cover. They were 9.5 cm wide, 12.5 cm long and 13.5 cm high. A stainless steel lever 2 cm wide, protruding 3 cm inside the cage, operated by a force of 7 to 8 g, was mounted on each front panel. To the left of the lever was a 3 cm aperture through which the mouse could drink from the cup of a liquid dipper. Each of the 8 chambers was enclosed within a sound-attenuating cubicle. When they were 22 weeks old, eight animals per sex and per group spent one hour each in the box, during which the number of lever presses was recorded. Each lever press activated an empty dipper and turned off the house light for 10 sec without any further consequences.

(4) Open field. The field comprised a surface of 0.25 m^2 divided into 16 squares. The mouse was placed in the center and its activity recorded for 3 minutes. Several different measures were taken: latency between placing the mouse and the first movement of its four paws; number of squares entered with four paws; rearing frequency; center crossings; grooming episodes; and number of boluses. After each mouse, the boluses were removed and the field cleaned with wet towels and dried. Three different groups of 6 mice per dose and sex were tested in the field at 30, 150 and 180 days of age.

Operant testing. The mice were selected randomly from different litters (4 males and 4 females per dose group). The training started when they were 20 weeks old. They were housed one per cage, food deprived, and maintained between 80 and 90% of their free-feeding weights. The 8 test chambers were described above. Each box was connected to a PDP 8/E computer (Digital Equipment Corporation) programmed to deliver stimuli and to collect lever presses recorded as sequential interresponse times [23]. During a single 2- to 3-hour session, the mice were trained to press the lever to obtain 0.01 cc of evaporated milk (Carnation) for each lever press. At first, a full food dipper was presented at variable intervals with a mean of 1 minute. Independently, each lever press was immediately followed by food delivery. If 25 responses were emitted within a 15-minute period, the training procedure was discontinued by the computer program and replaced by a continuous reinforcement schedule (CRF or FR1) on which every response gave access to a drop of milk. Five additional sessions on CRF followed. A fixed ratio schedule of reinforcement (FR), on which the mice had to press the lever a specified number of times to obtain milk, was then substituted for the CRF schedule [9]. The size of the ratio was increased every 5 sessions in successive values of FR 5, 10, 20, 35, 60 and 80. The sessions ended either after 100 reinforcements or after a maximum of 60 minutes. The running rate of responding was calculated as the number of responses emitted per minute from the first lever press after the postreinforcement pause (following the reinforcement cycle) to the response producing milk delivery.

Statistical Evaluation

Weight differences were evaluated by one-way analysis of variance [24] for the preweaning period and with t-tests for the adult measures. When the same animal was tested in more than one spontaneous activity device, performances in both tests were analyzed with the Spearman rank correlation coefficient method [22]. A high correlation would mean that the score on one activity test predicts the score on another; a low not significant correlation means that prediction is no better than chance. Statistical analyses of the sponataneous activity data were performed by randomization tests based on one-way ANOVA for 3-group comparisons [8]. Randomization tests rather than conventional parametric procedures were adopted because of the typical inhomogeneity of the data. Additional multivariate randomization tests [8; Gabriel, personal communication) were performed on the operant data. The accepted level of significance was $p<0.05$ (two-tailed test). Combined assessment of all the spontaneous activity values of both experiments was performed using the normal curve method of combining results from independent data [6].

RESULTS

There were no differences in weight between control and drug-treated offspring throughout the nursing period. No ex-

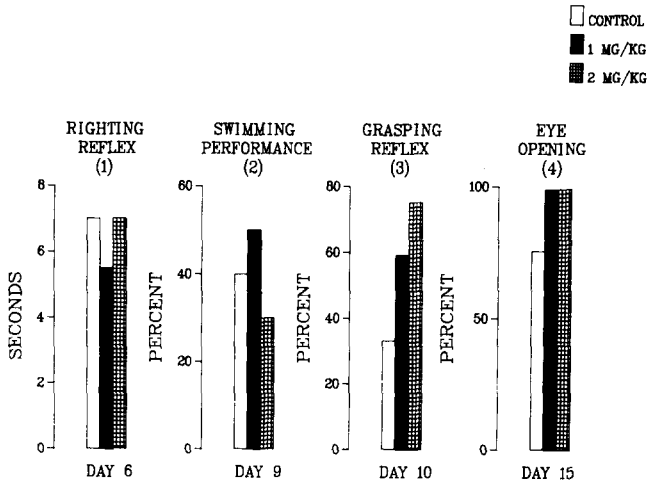

FIG. 1. Developmental indices measured in BALB/c mice. The animals received 0, 1 and 2 mg/kg of haloperidol from postnatal day 4 to 21 (open, solid and grid bars, respectively). (1) Righting reflex: Median time spent to return to a supine position on day 6. Two pups per litter were tested. (2) Swimming performance: Total percentage of pups able to swim straight on day 9. Two pups per litter were observed. (3) Grasping reflex: Proportion of pups per litter able to grasp the mesh on day 10. Six litters per group were tested. (4) Eye opening: Proportion of eyes open per litter on day 15.

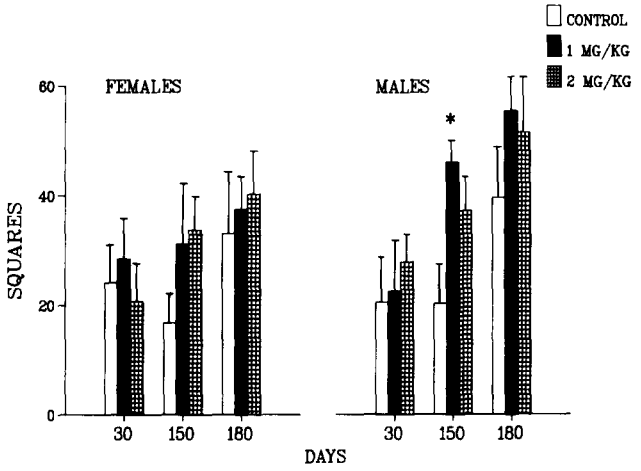

FIG. 2. Number of squares entered in the open field by BALB/c mice at 30, 150 and 180 days of age. On the left are the females; on the right, the males. The number of squares entered (ordinate) is plotted against time. The mice received 0, 1 and 2 mg/kg of haloperidol from postnatal day 4 to 21 (represented respectively by open, solid and grid bars). Each bar shows the mean±S.E. of 6 mice. *$p<0.05$.

cess mortality attributable to the drug treatment was recorded. The developmental indices are shown in Fig. 1. Righting reflex on day 6 and swimming performance on day 9 were similar in all groups. More experimental than control pups could grasp the mesh on day 10; $p=0.18$ by randomization test. There was a slight, but not statistically significant ($p=0.093$ by the same statistic) acceleration in eye opening in the haloperidol-treated pups compared to controls.

TABLE 1

p VALUES OF THE SPONTANEOUS ACTIVITY TESTING

	BALB/c		Swiss/Webster	
	Females	Males	Females	Males
Activity cage	0.77*	0.26	0.55	0.39
Operant chamber	0.62	0.32	0.57	0.58
Circular alley	0.31	0.25	0.15	0.54
Open field				
30 days	0.78	0.74	0.22	0.33
3 or 5 months	0.28	0.03	0.01	0.54
6 months	0.85	0.44	0.02	0.02

*Each p value (two-tailed test) was calculated by 3-group comparison randomization test among the performances of the animals which received 0, 1 and 2 mg/kg of haloperidol during nursing.

The statistical p-values of the spontaneous activity testing are shown in Table 1. Each value was calculated by randomization test ANOVA of the performance data of the 3 groups of animals that received 0, 1 and 2 mg/kg of haloperidol during nursing. Low p values reflect a haloperidol treatment effect. At 6 months of age, all the offspring had similar weights. No statistically significant treatment effect could be detected in the activity cage, the circular alley and the operant chamber although haloperidol-exposed males displayed a consistently enhanced locomotor activity compared to controls. The results obtained in the open field are presented in Fig. 2. At 30 days of age, neither experimental males nor females could be differentiated from their controls. When placed in the field at 150 days of age, however, drug-treated males were more active than controls ($p=0.03$ by randomization test). This was accompanied by an increased rearing frequency and center crossing ($p=0.02$ by randomization test for center crossings). Differences among female dose groups were not statistically significant. When an animal was used more than once, the influence of the first test on the results of a second was measured with the Spearman correlation coefficient test. The correlation coefficients ranged from $-.09$ to .54 and did not reach the 0.05 level of statistical significance.

There were no differences among the groups during the acquisition of the fixed ratio schedule. Figure 3 shows the rate of responding (number of responses per minute) emitted by the mice on each of the ratio values. Control and experimental animals of both sexes exhibited about the same rate of responding at ratio values up to FR35. Beyond that point, the group means diverged, but the differences were not statistically significant.

EXPERIMENT 2

METHOD

The subjects were 24 pregnant Swiss/Webster mice (Blue Spruce Farms). Drug procedure, preweaning behavioral assessment and postweaning behavioral methods were identical to those described for Experiment 1. The mice were placed in the open field at 30, 90 and 180 days of age. In the other 3 spontaneous activity devices, testing was conducted when the offspring were 3 months old. Six to eight mice per dose group and sex (with no more than one male and one

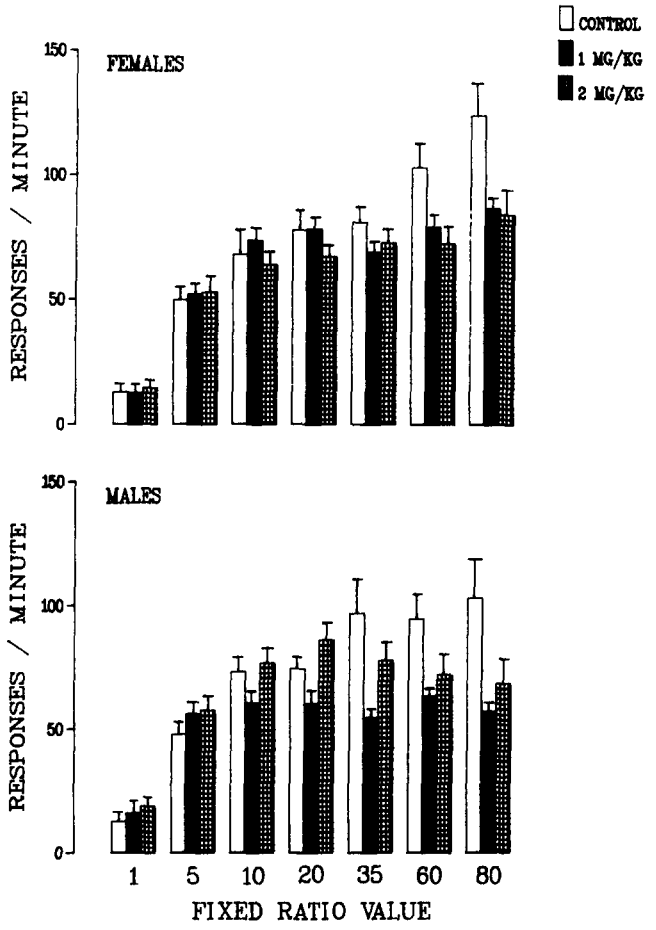

FIG. 3. Running rates of BALB/c females (top panel) and males (bottom panel) maintained on a fixed ratio schedule of reinforcement. Abscissa: ratio size; ordinate: number of responses per minute. The mice received 0, 1 and 2 mg/kg of haloperidol during nursing (respectively, open, solid and grid bars). Each bar represents the mean±S.E. of mice per group and sex.

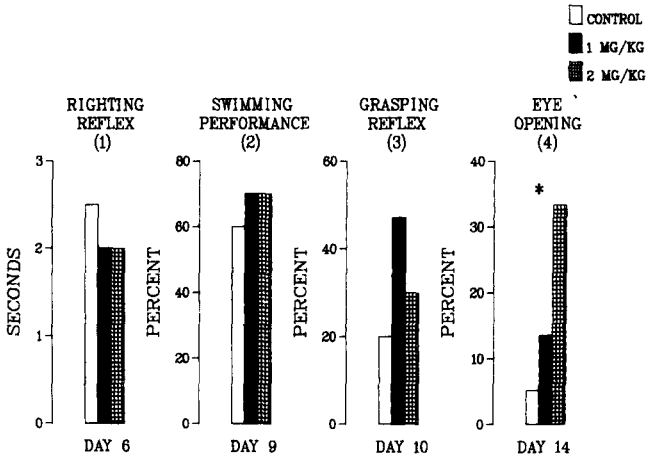

FIG. 4. Developmental indices measured in Swiss/Webster mice. The animals received 0, 1 and 2 mg/kg of haloperidol from postnatal day 4 to 21 (open, solid and grid bars, respectively). (1) Righting reflex: Medians of the time spent to return to a supine position on day 6. Two pups per litter were tested. (2) Swimming performance: Total percentage of pups able to swim straight on day 9. Two pups per litter were observed. (3) Grasping reflex: Proportion of pups per litter able to grasp the mesh on day 10. Six litters per group were tested. (4) Eye opening: Proportion of eyes open per litter on day 14. *$p<0.05$.

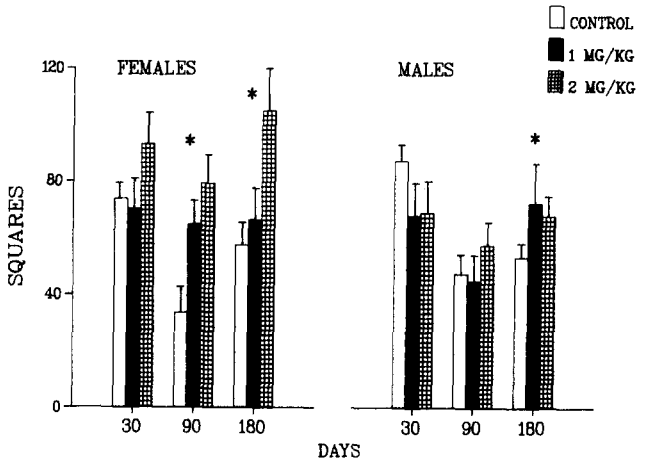

FIG. 5. Number of squares entered in the open field by Swiss/Webster mice at 30, 90 and 180 days of age. On the left are the females; on the right, the males. The number of squares entered (ordinate) is plotted aginst time. The mice received 0, 1 and 2 mg/kg of haloperidol from postnatal day 4 to 21 (represented respectively by open, solid and grid bars). Each bar shows the mean±S.E. of 6 to 8 mice. *$p<0.05$.

female for each litter) were tested in each apparatus. Thirty-three mice were tested in at least three different apparatuses, 25 in two, and 58 were used only once. In the activity cage, 3 mice were tested simultaneously. Training on the fixed ratio schedule started when the offspring (4 males and 4 females per group) were 3 months old. The successive ratio values were 5, 10, 20, 35, 60, 80, and 110.

RESULTS

As in Experiment 1, there were no differences among the groups in offspring weight and mortality throughout nursing. Figure 4 shows that righting reflex and swimming performance were about the same in each group. Similarly to BALB/c mice, more experimental animals could cling to the mesh ($p=0.18$; not statistically significant). The haloperidol-treated offspring also opened their eyes earlier than did their controls ($p=0.03$ by randomization test).

After weaning, all groups of mice were similar in weight at 30 days, and at 3 and 6 months of age. Data from the activity cage, the operant chamber and the circular alley showed no signficant differences among treatment groups. However, haloperidol-exposed females in the circular alley and males in the activity cage displayed more activity than controls (Table 1). When placed in the open field at 30 days of age, all the mice (male and female) crossed about the same number of squares (Fig. 5). At 90 days of age, the experimental females were more active than the controls ($p=0.01$ by randomization test). They also exhibited a greater number of rearings ($p=0.004$ by the same statistics). At 180 days, the

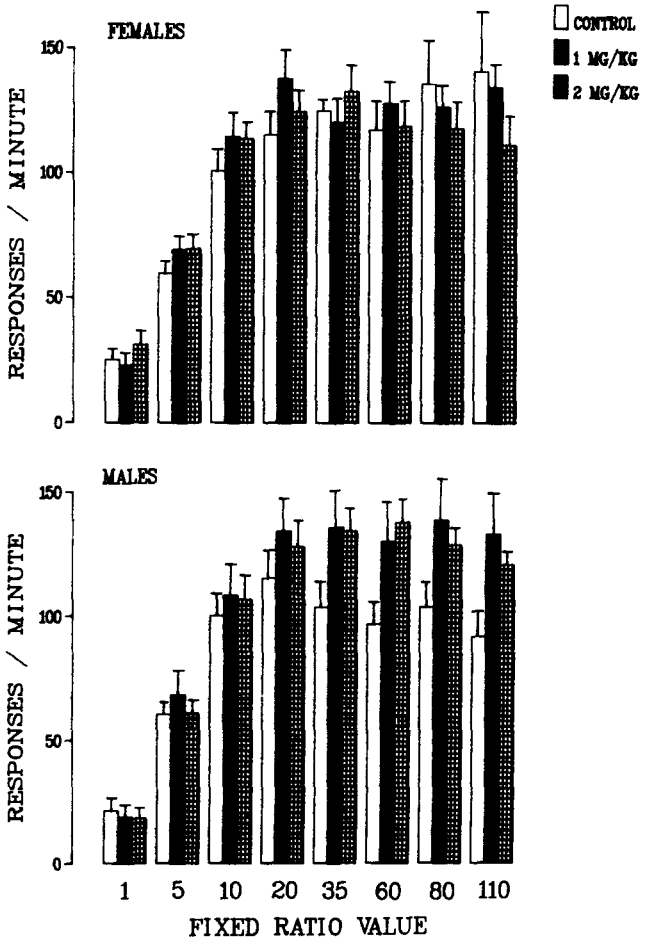

FIG. 6. Running rates of Swiss/Webster females (top panel) and males (bottom panel) maintained on a fixed ratio schedule of reinforcement. Abscissa: ratio size; ordinate: number of responses per minute. The mice received 0, 1 and 2 mg/kg of haloperidol during nursing (respectively, open, solid and grid bars). Each bar represents the mean±S.E. of 4 mice per group and sex.

higher incidence of squares crossed by haloperidol females was still apparent and was accompanied by more rearings and center crossings ($p=0.02$, 0.02 and 0.03 by randomization tests, respectively, for squares crossed, rearings and center crossings). The same pattern of elevated activity was also present in males ($p=0.02$ and 0.03 by randomization test, respectively, for squares and rearings). As in Experiment 1, the effects of repeated testing in the same animal were measured with the Spearman rank coefficient of correlation and the obtained coefficients were not statistically significant.

No treatment effects could be detected during fixed ratio acquisition. Figure 6 shows that females pretreated with haloperidol or distilled water emitted about the same number of lever presses at all fixed ratio values. In experimental males, however, there was a trend (not statistically significant) for responding at higher rates than controls after FR20. Two males in the 1 mg/kg group and one in the 2 mg/kg group were responsible for that trend: they responded at a much higher rate than any other mice.

Combined Results

We combined all the spontaneous activity values of both experiments and applied the normal curve method for combining results from independent data [6,20]. This method determines a z-score value by the following formula:

$$z = \frac{\text{Mean} - 0.50}{0.2887/\sqrt{n}}$$

where mean represents the mean of the n probability values. The normal curve table gives the overall p value. The assumption of statistical independence was not violated because the correlations among procedures were not significant. This procedure yielded an overall $p=0.043$.

GENERAL DISCUSSION

Daily injections of haloperidol during postnatal days 4 to 21 caused little change in growth and reflex development. After weaning, there were still no discrepancies in growth among the different groups. Behavioral assessment, however, revealed that early treatment exerted significant effects on activity level in adulthood.

The manifestation of drug effects depended on the age of the animals when tested, the particular test and performance measures, and the sex or strain.

(1) Age: No behavioral effect in either strain could be detected in the open field at 30 days of age. Aftermaths of drug treatment appeared only later and persisted until the mice were at least 6 months old.

(2) Test: Activity measures were not uniformly affected by the drug treatment. It is recognized that what is generally referred to as "spontaneous activity" comprises many classes of motor acts which can be differentially sensitive to drug effects [17]. Such diversity was cogently illustrated in the current study: the open field was the best method to differentiate drug treatment effect.

(3) Sex or strain: The operant schedule data showed a tendency for differential effects depending on the strain and the sex of the animal tested. Experimental BALB/c males lowered their rates of responding; their Swiss/Webster counterparts increased them. Experimental Swiss/Webster females displayed no change in lever pressing compared to controls although males of the same strain increased it.

In these experiments, the performance obtained in one test did not affect the performance obtained in a second test. Absence of intertest effects between different behavioral test procedures such as a shuttle box, open field, T-maze, swimming test, etc., has been also reported by Jensh *et al.* [13]. These observations have important implications for developmental pharmacology and toxicology because using the same subject in several tests decreases the cost and work involved in an experimental protocol.

This study also emphasizes common problems of statistical assessment. Many results did not reach conventional statistical significance because of the small number of animals used and because of marked variability among animals. Such variability is often encountered in developmental pharmacology and toxociology, especially at dose levels producing subtle effects. Differences in sensitivity are amplified, groups become inhomogeneous, and different statistical treatments than those traditionally used are called for. For this reason, we compared the 3 dose groups with randomization tests, which are more appropriate than parametric tests when only a few animals respond to the

treatment [7,12]. Although the application of these tests yielded some significant p values, many did not reach the 95% confidence level although suggesting parallel effects. To analyze these trends further and evaluate their overall significance, we combined the results of all the activity measures of both experiments as explained at the end of the Results section. The obtained overall $p=0.043$ suggests that the trends described did not occur by chance alone and that, indeed, neonatal haloperidol treatment induced subtle changes in adult behavior, mainly in increasing activity level.

This finding agrees with other experiments. Fonseca *et al.* [10] and Spear *et al.* [25] observed enhanced activity in an open field after either direct injection of haloperidol to the pups or maternal administration during gestation and nursing. In response to a dose of apomorphine and/or d-amphetamine, offspring of females treated with haloperidol during gestation were less sensitive to these drugs than controls when tested early after weaning [19, 21, 25]. However, if the offspring received haloperidol after birth, directly or through maternal milk, their response to apomorphine was enhanced compared to controls [3,19]. Although the behavioral response to pre- and postnatal exposure to haloperidol seems to be similar, the results obtained after d-amphetamine and apomorphine suggest that the mechanism of action of haloperidol probably differs depending on the start of the exposure period. The effects of postnatal administration most resembled the activity increases observed after withdrawal from chronic treatment in adult animals [1, 2, 16, 26, 28]. Similar results also have been observed 48 hours after withdrawal from fluphenazine in rats treated through gestation up to 32 weeks after birth [27]. In these experiments, behavioral assessments were performed in the first 10 to 15 days after cessation of drug treatment. In our experiment, however, weeks or months elapsed between the end of treatment and subsequent testing. Our results indicate that the behavioral consequences of early treatment with haloperidol are prolonged, if not permanent, and do not reflect an acute response to haloperidol withdrawal. Such effects may be related to the enduring haloperidol sensitivity observed in monkeys after the end of treatment [29,30].

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