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Dose Dependency of Sex Differences in the Effects of Repeated Haloperidol Administration in Avoidance Conditioning in Mice

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ARENAS, M. C., C. VINADER-CAEROLS, S. MONLEÓN, A. PARRA AND V. M. SIMÓN. *Dose dependency of sex differences in the effects of repeated haloperidol administration in avoidance conditioning in mice.* PHARMACOL BIOCHEM BEHAV **62**(4) 703–709, 1999.—Sex differences in the effects of haloperidol in active avoidance conditioning in mice have previously been found in various studies carried out in our laboratory. Males were more affected than females by the disruptive effects of this neuroleptic. The work described here broadens the study of these sex differences to higher doses of haloperidol (0.1 and 0.2 mg/kg) using a repeated administration schedule (5 days). The results did not show sex differences in the deteriorating effects of this dopamine antagonist in the escape-avoidance response, but a tendency in the number of nonresponses was observed in the same direction as former results: male animals were more sensitive than females to the inhibitory effect of the low dose of haloperidol. It is concluded that the appearance of sex differences in the effects of haloperidol on active avoidance conditioning is a dose-dependent phenomenon. © 1999 Elsevier Science Inc.

Active avoidance Haloperidol Mice

IT is well established that haloperidol produces a dose-dependent impairment in the acquisition and performance of active avoidance conditioning (3,10,12,15,20,22,28,29,31–36,40–42), which is not only due to a deterioration of motor behavior (7). These effects of haloperidol have been explored on escape-avoidance responses using acute administration (3,6,15,22,28, 29,31–35,40–42) and on the learning of a conditioned avoidance response (CAR) using repeated administration (7,8,10,12,36).

Moreover, sex differences in the effects of neuroleptics have been described in previous studies in our laboratory (6–9,28–30). We found these in a unique training session of an active avoidance task, using a dose of haloperidol that clearly deteriorates avoidance responses [0.25 mg/kg; (36)]. We observed that male mice presented fewer escape responses and more nonresponses than female animals, while activity measures did not show these sex differences (6,28). In a more recent study, these sex differences were evaluated in a unique training session of active avoidance using several doses of haloperidol (0.075, 0.25, and 0.75 mg/kg, IP). Males made significantly fewer escapes and more nonresponses than females in a dose-dependent manner: a positive correlation was obtained between the doses of haloperidol and the sex differences observed in these measures. The higher the dose, the greater the sex differences (29).

Another study was carried out to further evaluate sex differences in acquisition and performance of active avoidance in mice, in which the drug's effects on motor behavior were also controlled (7). For this purpose, the effects of 0.075 mg/kg of haloperidol for 5 days on the acquisition of a conditioned avoidance response were explored. The results showed sex differences in the effects of haloperidol in the avoidance conditioning. Males made fewer avoidance responses, and their escape latencies were longer than those of their saline controls (7). These differences also agree with findings using a DRL 15-s schedule (39). The dose used in our previous investigation on the subchronic effect of haloperidol on active avoidance in males [0.075 mg/kg/day; (7)], although capable of deteriorating the performance of the males, did not significantly affect

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female conditioning. In view of this, the aim of the present study was to explore if moderately higher doses of haloperidol (0.1 and 0.2 mg/kg/day) were capable of impairing conditioning of females and if, at these doses, the sex differences were still evident. For this purpose, the haloperidol effects in the acquisition of avoidance conditioning were evaluated during 5 training days following a similar procedure as that employed by Arenas et al. (7).

METHOD

Subjects

Thirty female and 30 male OF1 mice from CRIFFA (Lyon, France), weighing between 24–28 and 30–42 g, respectively, at the start of the experiment, were used as experimental animals. They arrived in the laboratory at 42 days of age and were housed, for 11 days, in unisexual groups of five animals in translucent plastic cages (25 × 25 × 14.5 cm) under a reversed light–dark cycle (lights off: 0730–1930 h, local time) and controlled room temperature (22 ± 3°C). All the experimental procedures were in compliance with the European Communities Council Directive of 24 November 1986 (86/609/EEC), and the equivalent Spanish Laws.

Drug

The doses of haloperidol (Haloperidol® Syntex Latino, Spain) 0.1 and 0.2 mg/kg were administered IP in a volume of 0.01 ml/g body weight. The drug was diluted with 0.9% saline to obtain the appropriate concentrations. Controls received 0.9% saline alone in the same volume.

Apparatus

Two computerized two-way shuttle-boxes (Shuttle Scan, Model SC-II, Omnitech Electronics, Inc., Columbus, OH) described in detail elsewhere (6) and the RMS V.2.02 software of Omnitech Electronics were used.

Procedure

After the period of 14 days of adaptation to the laboratory, the subjects of each sex were randomly assigned to one of three groups ($n = 10$): saline (S), haloperidol 0.1 mg/kg (H1), and haloperidol 0.2 mg/kg (H2). Each animal was tested in the shuttlebox 30 min after injection for 5 consecutive days. The test comprised: (a) 3 min of adaptation to the apparatus, in which animals explored the box and moved freely; (b) 30 trials of two-way escape-avoidance (intertrial interval, 30 ± 10 s). Each trial consisted of the presentation of a light (6 W) in the compartment occupied by the mouse, which, after 5 s, was overlapped by a 0.3-mA foot shock of 10 s in duration. An avoidance response was defined as a crossing to the opposite side during the period of illumination, an escape as a crossing when the shock was on, and a nonresponse as the absence of crossing. All tests were run between the second and the ninth hour of the dark phase of the light cycle. The following two groups of behavioral parameters were computed: (a) measures of conditioning: number of avoidances, number of escapes, number of nonresponses, latencies of avoidance responses (Lat-A) and latencies of escape responses (Lat-E); (b) activity measures: number of crossings during the adaptation period (Adapt-Cross), and number of crossings during intertrial intervals (ITI-Cross).

Statistical Analyses

Nonparametric Kruskal–Wallis test was used to assess the variance of the behavioral measures (escapes, avoidances, nonresponses, crossings during the adaptation period, and crossings during ITIs) over different groups. Subsequently, appropriate paired comparisons were carried out using Mann–Whitney *U*-tests to contrast the behavior among different treatment groups. Latencies of avoidance responses and latencies of escape responses were subjected to analysis of variance (ANOVA) for each day, with sex and treatment as the main factors, supplemented by Newman–Keuls pairwise comparisons and tests of simple main effects.

RESULTS

Table 1 summarizes the results for measures of conditioning as well as for activity. The Kruskal–Wallis and ANOVA analyses are shown in Tables 2 and 3, respectively.

Number of Avoidances

In males, the S group made more avoidances than the H1 and H2 groups on days 2, 3, 4 (Us < 7, ps < 0.005) and 5 (Us < 14, $p < 0.05$). In females, the S group made more avoidances than the H1 group on days 2, 3, 4, and 5 (Us < 19, ps < 0.05), and than the H2 group on days 1 ($U = 22$, $p < 0.05$), 2, 3, 4, and 5 (Us < 10, ps < 0.005); there was also a significant difference between the H1 and H2 groups on day 4 ($U = 17.5$, $p < 0.05$).

Number of Escapes

In males, the S group made more escapes than the H2 group on day 1 ($U = 6.5$, $p < 0.005$); moreover, the H1 group made more escapes than the H2 on days 1, 2, and 4 (Us < 23; ps < 0.05). In females, the S group made more escapes than the H2 group on days 1 ($U = 7$, $p < 0.005$) and 2 ($U = 11$, $p < 0.05$); and the H1 group more than the H2 on days 1 and 4 (Us < 16.5, ps < 0.05) and 2 ($U = 9$, $p < 0.005$).

Number of Nonresponses

In males, the S group made fewer nonresponses than the H2 group every day (days 1, 2, and 4, Us < 7.5, ps < 0.005; days 3 and 5, Us < 18.5, ps < 0.05); and the H2 group made less nonresponses than the H1 on days 1, 2, and 4 (Us < 20.5, ps < 0.05). In the females, the H1 group made more nonresponses than the S group on day 1 ($U = 22$, $p < 0.05$) and the H2 group more than S every day (days 1, 2, 4, and 5, Us < 8, ps < 0.005; day 3, $U = 11$, $p < 0.05$); the H2 group also made more nonresponses than the H1 on days 1 and 2 (Us < 10, ps < 0.005), 3 and 4 (Us < 16; ps < 0.05).

Number of Crossings During the Adaptation Period (Adapt-Cross)

In males, the S group made more crossings than the H1 (days 2 and 3, Us < 22, ps < 0.05) and H2 groups (days 1, 2, 3, and 4, Us < 16.5, ps < 0.05); and the H1 group also made more crossings in this period than the H2 on days 1, 2, 3, and 4 (Us < 20.5, ps < 0.05). In females, the S group made more crossings than the H1 on days 4 and 5 (Us < 19, ps < 0.05) and H2 every day (days 1 and 2, Us < 23, ps < 0.05; days 3, 4, and 5, Us < 2, ps < 0.005); moreover, the H2 group made less crossings than the H1 on days 1 and 2 (Us < 18.5; ps < 0.05), 3 and 4 (Us < 6.5; ps < 0.005).

Number of Crossings During Intertrial Intervals (ITI-Cross)

In males, the S group made more crossings than the H1 group on days 2, 4, and 5 (Us < 18, ps < 0.05) and 3 ($U = 10$;

TABLE 1

TOTAL NUMBER OF AVOIDANCES, ESCAPES, NONRESPONSES, CROSSINGS DURING THE ADAPTATION PERIOD (ADAPT-CROSS), AND CROSSINGS DURING IT IS (ITI-CROSS), AND MEAN LATENCIES OF ESCAPE (LAT-E) AND AVOIDANCE RESPONSES (LAT-A) WITH SD

		Males			Females		
Parameters	Days	Saline	Haloperidol (0.1 mg/kg)	Haloperidol (0.2 mg/kg)	Saline	Haloperidol (0.1 mg/kg)	Haloperiodol (0.2 mg/kg)
Avoidances	1	41	12	6	48	19	5†
	2	97	12*	7*	79	19†	3*
	3	123	18*	15*	92	13†	6
	4	127	11*	14*	101	33†	5*‡
	5	134	21†	16†	148	41†	21*
Escapes	1	199	164	64*‡	183	148	41*‡
	2	165	204	109‡	204	220	68§
	3	136	169	129	175	231	126‡
	4	120	200	95‡	181	212	113‡
	5	102	166	111	139	187	135
Nonresponses	1	60	124	230*‡	69	133†	254*§
	2	38	84	184*‡	17	61	229*§
	3	41	113	156†	33	56	168†‡
	4	53	89	191*‡	18	55	182*‡
	5	64	113	173†	13	72	144*
Adapt-Cross	1	96	82	38†‡	78	80	34†‡
	2	190	117†	61†‡	148	139	29†‡
	3	181	118†	56†‡	162	108	18*§
	4	196	154	69†‡	233	106†	27*§
	5	162	102	77	230	114†	53*
ITI-Cross	1	327	140	66†	332	167	60
	2	399	142†	58*	463	108	64
	3	438	107*	115†	491	89†	74†
	4	456	129†	81*	480	182	79†
	5	387	111†	114†	505	125†	89†
Lat-E	1	8.58±1.53	9.40 ± 1.23	9.51 ± 1.47	8.19 ± 1.09	9.65 ± 0.89	8.62 ± 1.28
	2	7.45±1.90	8.70 ± 1.55	9.14 ± 1.66	7.17 ± 1.06	7.84 ± 1.28	9.65 ± 1.12
	3	7.13±1.65	8.85 ± 1.72	8.41 ± 1.29	7.46 ± 1.54	8.15 ± 1.90	9.79 ± 2.08
	4	7.23±1.57	8.78 ± 1.93	8.65 ± 1.09	7.13 ± 1.26	7.97 ± 1.44	9.71 ± 1.70
	5	7.42±1.79	8.86 ± 1.49	9.26 ± 1.15	7.09 ± 1.50	8.07 ± 1.56	9.11 ± 1.27
Lat-A	1	2.46±0.81	2.09 ± 1.19	2.20 ± 1.23	2.13 ± 1.08	1.83 ± 1.30	0.81 ± 0.08
	2	2.27±0.44	1.36 ± 0.78	2.37 ± 0.80	2.79 ± 1.16	1.70 ± 1.03	1.77 ± 2.63
	3	2.47±0.73	2.21 ± 0.84	1.66 ± 1.14	2.67 ± 0.95	2.65 ± 1.52	4.28 ± 2.21
	4	2.31±0.85	2.61 ± 0.93	2.23 ± 1.31	3.11 ± 0.61	1.91 ± 1.42	1.12 ± 1.16
	5	2.55±0.57	2.68 ± 1.47	2.38 ± 0.44	2.76 ± 0.62	2.90 ± 0.84	2.05 ± 1.14

Compared with saline: *$p < 0.07$;
† $p < 0.05$ (Mann-Whitney U test).
Compared with haloperidol (0.1 mg/kg):
‡$p < 0.05$;
§$p < 0.01$ (Mann-Witney U test).

$p < 0.005$) and the H2 every day (days 1, 3, and 5, Us < 20.5, ps < 0.05; days 2 and 4, Us < 8, ps < 0.005). In females, the S group made more crossings than H1 on days 3 and 5 (Us < 14.5, ps < 0.05) and H2 on days 3, 4, and 5 (Us < 13, ps < 0.05).

Latency of Escape Responses (Lat-E)

The ANOVA did not show sex differences in lat-E. Treatment was significant in this measure. And simple effects showed that treatment was significant in males on day 2, $F(2, 53) = 3.232$, $p < 0.05$; day 3, $F(2, 53) = 3.249$, $p < 0.05$; day 4, $F(2, 54) = 4.002$, $p < 0.05$; and day 5, $F(2, 53) = 5.602$, $p < 0.01$; as well as in females on day 2, $F(2, 53) = 7.796$, $p < 0.005$; day 3, $F(2, 53) = 4.421$, $p < 0.05$; day 4, $F(2, 54) = 6.328$, $p < 0.005$; and day 5, $F(2, 53) = 5.518$, $p < 0.01$.

Latency of Avoidance Responses (Lat-A)

Significant differences were observed only on days 3 and 4 for the variables sex and treatment, respectively (see Table 3). On day 3, females had longer lat-A than males. The simple main effects also showed significant differences between males and females in the groups H2, $F(1, 35) = 10.237$, $p = 0.003$. And on day 4, the variable treatment was significant. The post hoc analysis showed that saline mice had longer lat-A than the H2 groups ($p < 0.05$). The simple main effects also revealed that treatment was significant in the female mice, $F(2, 39) = 5.878$, $p = 0.006$.

DISCUSSION

In the present experiment the effects of 0.1 and 0.2 mg/kg/day of haloperidol on an escape-avoidance task were studied

TABLE 2
NONPARAMETRIC STATISTICAL ANALYSIS (KRUSKAL–WALLIS TEST)

Parameters	All Animals		Males		Females	
Avoidances						
Sex	H < 1	NS				
Treatment	$H = 33.5$	$p < 0.001$	$H = 18.2$	$p < 0.001$	$H = 15.6$	$p < 0.001$
Treatment × Day 1	$H = 10.1$	$p < 0.006$	$H = 4.6$	NS	$H = 6.1$	$p < 0.05$
Treatment × Day 2	$H = 31.6$	$p < 0.001$	$H = 17.7$	$p < 0.001$	$H = 13.8$	$p < 0.001$
Treatment × Day 3	$H = 29.1$	$p < 0.001$	$H = 15.6$	$p < 0.001$	$H = 13.4$	$p < 0.001$
Treatment × Day 4	$H = 28.9$	$p < 0.001$	$H = 16.2$	$p < 0.001$	$H = 15.4$	$p < 0.001$
Treatment × Day 5	$H = 25.6$	$p < 0.001$	$H = 11.5$	$p < 0.003$	$H = 12.9$	$p < 0.002$
Escapes						
Sex	H < 2	NS				
Treatment	$H = 16.1$	$p < 0.001$	$H = 7.1$	$p < 0.03$	$H = 10.0$	$p < 0.007$
Treatment × Day 1	$H = 27.4$	$p < 0.001$	$H = 13.9$	$p < 0.001$	$H = 13.1$	$p < 0.001$
Treatment × Day 2	$H = 17.5$	$p < 0.001$	$H = 5.6$	NS	$H = 12.8$	$p < 0.002$
Treatment × Day 3	$H = 5.9$	NS	$H = 1.5$	NS	$H = 5.3$	NS
Treatment × Day 4	$H = 13.0$	$p < 0.002$	$H = 5.9$	NS	$H = 7.1$	$p < 0.05$
Treatment × Day 5	$H = 6.1$	$p < 0.05$	$H = 4.0$	NS	$H = 2.2$	NS
Nonresponses						
Sex	H < 3	NS				
Treatment	$H = 33.2$	$p < 0.001$	$H = 14.2$	$p < 0.001$	$H = 19.0$	$p < 0.001$
Treatment × Day 1	$H = 33.2$	$p < 0.001$	$H = 16.6$	$p < 0.001$	$H = 16.8$	$p < 0.001$
Treatment × Day 2	$H = 29.9$	$p < 0.001$	$H = 11.9$	$p < 0.003$	$H = 17.8$	$p < 0.001$
Treatment × Day 3	$H = 18.6$	$p < 0.001$	$H = 8.3$	$p < 0.02$	$H = 10.8$	$p < 0.004$
Treatment × Day 4	$H = 28.7$	$p < 0.001$	$H = 12.4$	$p < 0.002$	$H = 16.1$	$p < 0.001$
Treatment × Day 5	$H = 16.5$	$p < 0.001$	$H = 6.2$	$p < 0.05$	$H = 10.5$	$p < 0.005$
Adapt-Cross						
Sex	H < 2	NS				
Treatment	$H = 33.6$	$p < 0.001$	$H = 15.3$	$p < 0.001$	$H = 18.1$	$p < 0.001$
Treatment × Day 1	$H = 15.8$	$p < 0.001$	$H = 9.1$	$p < 0.02$	$H = 7.2$	$p < 0.03$
Treatment × Day 2	$H = 16.4$	$p < 0.001$	$H = 10.6$	$p < 0.005$	$H = 8.2$	$p < 0.02$
Treatment × Day 3	$H = 25.5$	$p < 0.001$	$H = 10.9$	$p < 0.004$	$H = 17.3$	$p < 0.001$
Treatment × Day 4	$H = 31.3$	$p < 0.001$	$H = 11.6$	$p < 0.003$	$H = 20.7$	$p < 0.001$
Treatment × Day 5	$H = 20.4$	$p < 0.001$	$H = 5.4$	NS	$H = 14.7$	$p < 0.001$
ITI-Cross						
Sex	H < 1	NS				
Treatment	$H = 24.9$	$p < 0.001$	$H = 15.9$	$p < 0.001$	$H = 10.7$	$p < 0.005$
Treatment × Day 1	$H = 33.5$	$p < 0.001$	$H = 7.4$	$p < 0.03$	$H = 3.7$	NS
Treatment × Day 2	$H = 33.5$	$p < 0.001$	$H = 13.1$	$p < 0.001$	$H = 4.7$	NS
Treatment × Day 3	$H = 33.5$	$p < 0.001$	$H = 11.8$	$p < 0.003$	$H = 10.6$	$p < 0.005$
Treatment × Day 4	$H = 33.5$	$p < 0.001$	$H = 13.6$	$p < 0.001$	$H = 7.4$	$p < 0.03$
Treatment × Day 5	$H = 33.5$	$p < 0.001$	$H = 7.4$	$p < 0.03$	$H = 12.8$	$p < 0.002$

in male and female mice during 5 consecutive days. The results obtained are a further example of the well-known inhibitory effect of haloperidol on conditioned responses, specifically, on escape-avoidance conditioning (3,6–8,10,12,15,20,22, 28,29,31–36,40–42). Both doses of drug decreased the number of avoidance and increased the latencies of escape responses, but only the highest dose decreased the number of escape responses and increased the number of nonresponses. The decrease found in spontaneous motor activity also confirms other findings well documented in the literature (1,2,4–8,11,17–19,22–24,26,28,29,37,40).

In a previous study carried out with the same experimental procedure (7), the dose of 0.075 mg/kg/day of haloperidol was found to impair the acquisition of active avoidance conditioning in male but not in female animals. In the present experiment, both doses of haloperidol (0.1 and 0.2 mg/kg/day) impaired female performance in a dose-dependent manner. The smallest dose decreased their avoidances, while the highest decreased both the number of escapes as well as the number of avoidances, and also increased the number of nonresponses. Concerning sex differences in the effects of haloperidol, a tendency was observed in the number of avoidances and nonresponses in the same direction as in former works: male mice were more sensitive than females to the inhibitory effect of both doses of haloperidol, but no significant sex differences were found (see Fig. 1). Regarding the repeated administration of haloperidol in this and previous, the sex differences have been found to be significant with a dose of 0.075 mg/kg/day, a tendency remained with 0.1 mg/kg/day, and disappeared with 0.2 mg/kg/day. Therefore, the appearance of sex differences in the effects of haloperidol on active avoidance conditioning may be considered as a dose-dependent phenomenon, as depicted in Fig. 2. This shows that the dose-response functions in male and female subjects are not parallel. Male performance is decreased at a lower dose than that necessary to decrease female performance. In general, it seems

TABLE 3
ANALYSIS OF VARIANCE (ANOVA)

Parameters	Days	Main Effects		
		Sex	Treatment	Sex × Treatment
Lat-E	1	$F(1, 52) = 1.23$, NS	$F(2, 52) = 2.77$, NS	$F(2, 52) < 1$, NS
	2	$F(1, 53) < 1$, NS	$F(2, 53) = 10.38$, $p < 0.001$	$F(2, 53) < 1$, NS
	3	$F(1, 53) < 1$, NS	$F(2, 53) = 6.09$, $p < 0.01$	$F(2, 53) = 1.59$, NS
	4	$F(1, 54) < 1$, NS	$F(2, 54) = 8.81$, $p < 0.001$	$F(2, 54) = 1.51$, NS
	5	$F(1, 53) < 1$, NS	$F(2, 53) = 10.61$, $p < 0.0001$	$F(2, 53) < 1$, NS
Lat-A	1	$F(1, 23) = 2.74$, NS	$F(2, 23) = 1.44$, NS	$F(2, 23) = 1.28$, NS
	2	$F(1, 28) < 1$, NS	$F(2, 28) = 2.52$, NS	$F(2, 28) < 1$, NS
	3	$F(1, 35) = 12.67$, $p < 0.005$	$F(2, 35) < 1$, NS	$F(2, 35) = 3.17$, NS
	4	$F(1, 39) < 1$, NS	$F(2, 38) = 3.87$, $p < 0.05$	$F(2, 38) = 3.11$, NS
	5	$F(1, 37) < 1$, NS	$F(2, 37) = 1.86$, NS	$F(2, 37) < 1$, NS

that the impairing effect of haloperidol is reached with a lower dose in males than in females, and, once this level is reached a further amount of drug does not lead to further impairing of performance. In fact, in the present experiment, there were no differences between the 0.1 and 0.2 mg/kg male groups, and indeed, such differences were found in the case of females, finding the higher effect in the highest dose.

The same sex differences in the effects of haloperidol (0.075 mg/kg) on the acquisition of a CAR has been found in mice when the retention of the response was evaluated in drug free animals at the end of the training period (7). Previous studies in rats have found the same relationship between the acquisition and performance phases (10,36), although it has also been observed that, in one-way avoidance learning, the acquisition impairment is not followed by poor performance in the absence of drug (16).

It must be noted that this dose-dependent phenomenon has also been observed with acute administration of haloperidol, but in the opposite direction: the sex differences were not found with 0.075 mg/kg, a tendency was observed with 0.25 mg/kg, and these differences were statistically significant with 0.75 mg/kg of haloperidol. Thus, the higher the dose, the greater the sex differences (6,29). Similar results have subsequently been found with acute administration of other neuroleptics (30). These different results in acute and repeated administration of haloperidol can be considered complementary rather than contradictory, taking into account that the doses used in acute treatment are too high to be repeatedly administered.

We consider that the number of avoidances is a more reliable measure of learning than avoidance latencies. In this work, with the exception of day 3, significant sex differences were not found in avoidance latencies. On this day, the female mice receiving the highest dose of haloperidol had statistically longer latencies than the male group; but these latencies were calculated with an extremely low number of avoidances (see Table 1). Moreover, the saline groups had significantly longer latencies than the haloperidol 0.2 mg/kg groups on day 4. Table 1 shows that, on this day, the female latencies of the saline group are longer than those of the 0.1 mg/kg group, and these are, in turn, longer than those of the 0.2 mg/kg group. These differences seem to be due to the higher number of avoidances in saline groups than in the groups of 0.1 mg/kg of haloperidol, and in turn, these were higher than those of the 0.2 mg/kg group.

As expected, haloperidol decreased spontaneous motor activity measured by the number of crossings during the adaptation period and ITIs. However, in an earlier study we have described more crossings in males than in females of saline groups (7), and in the present experiment these differences were not found. On the other hand, the sex differences in the effects of haloperidol found in measures of motor activity were in the opposite direction of the tendency observed in the conditioning measures: on day 4, the females treated with 0.2 mg/kg of haloperidol made significantly fewer crossings dur-

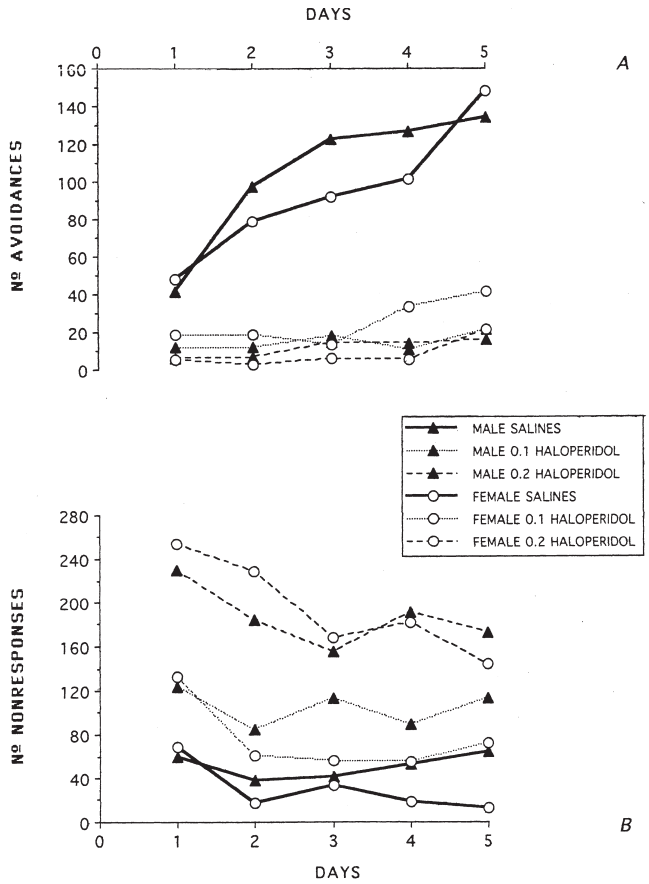

FIG. 1. Effects of haloperidol during acquisition in a two-way shuttle-box on: (A) number of avoidances, and (B) number of nonresponses. For significant differences see Table 1.

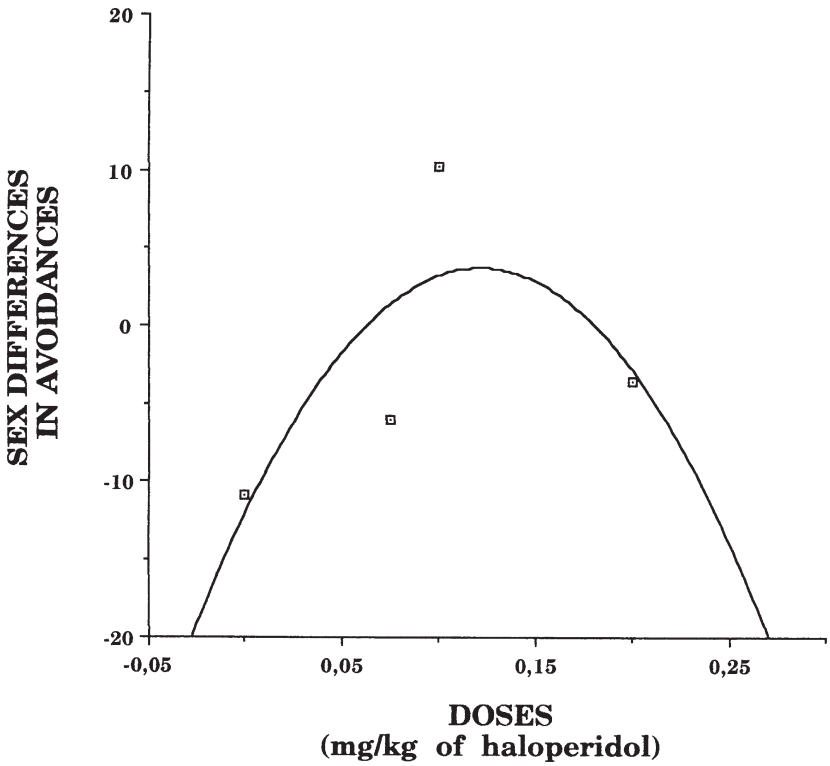

FIG. 2. Relationship between doses of haloperidol and sex differences in avoidances (mean number of avoidances in females minus mean number of avoidances in males), the best-fit quadratic function fitted to the data is based on the equation $y = -1740\,x^2 + 384x - 10.8$.

ing the adaptation period than males did. As pointed out in our previous studies (6–8,28,29), we considered that the mechanisms of action for disrupting effects on conditioned responses and on motor activity are different.

In summary, the doses of haloperidol (0.1 and 0.2 mg/kg/day) impaired, in a dose-dependent manner, the acquisition of active avoidance conditioning in female mice. Taking the results of the present study and those previously found in several experiments carried out in our laboratory (6–8,28,29) together, we may conclude that the appearance of sex differences in the effects of haloperidol on active avoidance conditioning in mice is a dose-dependent phenomenon: in repeated administration, these sex differences are observed with doses smaller than 0.1 mg/kg, and in a unique administration these are found with doses equal to or higher than 0.25 mg/kg.

Several explanations of the origin of these sex differences observed in the action of neuroleptics have been proposed. Three of them have been specially considered: the modulation of the central dopaminergic function by female hormones (oestrogens), pharmacokinetic differences, and different sensitivity to pain between male and female subjects [discussed with more detail in (29)]. The influence of oestrogens on the central dopaminergic transmission is the possibility that has received more widespread attention [for more detail see (9)]. A previous study from our laboratory provided some support that oestrogens, besides having an impairing effect on the learning of a CAR, exert a buffering action on the impairing effects of haloperidol on the acquisition of avoidance behavior (8).

Active avoidance conditioning has been considered a useful tool for selecting and studying antipsychotic drugs. Such drugs deteriorate the ability of animals to avoid shock at doses, which do not impair escape behavior. The usefulness of this test is due to the high correlation found between the capacity of dopaminergic antagonists to block avoidance responses and their therapeutic efficacy (13–15,21,25,27, 31,32, 36). The sex differences found with our studies in the avoidance conditioning may reflect the sex differences in the therapeutic and secondary effects of neuroleptics described in schizophrenic patients [e.g., (38)]. It is worth considering the possibility that if the pharmacological treatments were specifically determined according to the characteristics of each patient, the variable sex should be taken into account. Up to date, the magnitude of these differences has not led to sex-specific prescriptions.

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