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Sex Differences in Escape–Avoidance Response in Mice After Acute Administration of Raclopride, Clozapine, and SCH 23390

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MONLEÓN, S., C. VINADER-CAEROLS AND A. PARRA. *Sex differences in escape–avoidance response in mice after acute administration of raclopride, clozapine, and SCH 23390.* PHARMACOL BIOCHEM BEHAV **60**(2) 489–497, 1998.—Sex differences in the effects of haloperidol in the escape–avoidance response 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 herein extended the study of these sex differences to raclopride, clozapine, and SCH 23390, using several doses of each drug in acute administration. The results showed dose-dependent sex differences in the deteriorating effects of these dopamine antagonists in the escape–avoidance response. Male mice were more affected by the inhibitory effects of these drugs, showing fewer escape responses and more nonresponses than females. Sex differences were found with all three of the dopamine antagonists studied, indicating, therefore, that these differences do not depend on a unique type of dopaminergic receptor. The results obtained in motor activity, measured by the number of crossings during the adaptation period and the intertrial intervals, suggest that the motor effects are not the origin of these differences. It is concluded that, besides haloperidol, other dopamine antagonists also show sex differences in their behavioral effects in escape–avoidance response in mice, with males being more affected than females by the inhibitory action of these drugs. © 1998 Elsevier Science Inc.

Sex differences Active avoidance Learning Neuroleptics Raclopride Clozapine SCH 23390 Mice

ESCAPE–AVOIDANCE response has classically been considered a useful tool for selecting and studying antipsychotic drugs (13,14,17,33,47); such drugs disrupt the ability of animals to avoid shocks at doses that do not alter escape behavior (13,38,56). Many studies have shown that neuroleptics produce a dose-dependent impairment on the acquisition and performance of this active avoidance conditioning (2–5,7,9, 12,17,32,42,43,46,47,49,52,54,56,63–66).

Sex differences in the effects of neuroleptics have also been described in human subjects (18,31,37,41,55,57–59,61,62,67), as well as in several experimental procedures with animals (3,4, 6,11,15,19,34,42,43,45,53).

Sex differences in the effects of haloperidol in the escape–avoidance response in mice have previously been found in several studies carried out in our laboratory (3,4,42,43). In a unique training session of active avoidance after acute administration of 0.25 mg/kg IP of haloperidol, a dose that clearly deteriorates avoidance responses (56), OF1 male mice showed fewer escape responses and more nonresponses than females; while sex differences were not observed in motor activity, measured by the number of crossings during the adaptation period and intertrial intervals (3). Similar results have subsequently been found with BALB/c mice (42).

Another study was carried out to further evaluate sex differences in acquisition and performance of escape–avoidance response in mice, where the drug's effects on motor behavior were also controlled (4). For this purpose, the effects of daily administration (for 5 days) of 0.075 mg/kg of haloperidol on the acquisition of a conditioned avoidance response were explored. Forty-eight hours after the last drug administration,

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performance was evaluated in the drug-free subjects, and part of the saline-treated animals were tested under haloperidol. Residual effects of haloperidol on behavior are not usually found after this lapse of time (1,40). The results showed sex differences in the effects of haloperidol, both in the acquisition and the performance of the escape–avoidance response. Thus, males trained on the drug, and later testing drug free, made less avoidance responses, and their escape latencies were longer than those of their saline controls (4).

In a recent study, these sex differences were evaluated in a unique training session using several doses of haloperidol (0.075, 0.25, and 0.75 mg/kg, IP). Males made significantly less 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 (43).

The present study was designed to check the generality of the phenomenon, extending the study of these sex differences to other dopamine antagonists. For this purpose, three drugs were selected according to their affinity for D_1 and D_2 dopaminergic receptors: raclopride, highly selective D_2 dopamine receptor antagonist (24,25,44); clozapine, a nonselective antagonist with comparable D_1–D_2 affinities (10,16,25,26,50,51); and SCH 23390, a specific D_1 dopamine receptor antagonist (35,36). Three experiments were carried out using several doses of each drug in acute administration. The doses were chosen taking into account their particular capacity to reduce motor activity [calculated from unpublished data from our laboratory for raclopride and clozapine, and from (27) for SCH 23390]. The three selected doses of each drug reduced the spontaneous motor activity to approximately 55, 43, and 8% of that of saline controls (respectively for the low, the medium, and the high dose of each drug).

METHOD

Subjects

Forty female and 40 male OF1 mice from CRIFFA (Lyon, France), weighing between 24–28 g and 30–36 g, respectively, at the start of the experiment were used as experimental animals in each of the three experiments. They arrived in the laboratory at 42 days of age and were housed, for 13–14 days, in unisexual groups of five animals in translucent plastic cages ($25 \times 25 \times 14.5$ cm) under a reversed light–dark cycle (lights off: 0730–1930 h, local time) with food and water available ad lib and controlled room temperature (22 ± 2°C).

Drugs

The compounds used were raclopride tartrate (Astra, Sweden), clozapine (Research Biochemicals International RBI, USA), and R(+)SCH 23390 hydrochloride (RBI, USA). Taking into account their particular capacity to reduce motor activity, the equipotent doses selected were: 0.4, 1.2, and 3.6 mg/kg of raclopride (Experiment 1); 1.0, 3.0, and 9.0 mg/kg of clozapine (Experiment 2); 0.06, 0.2, and 0.6 mg/kg of SCH 23390 (Experiment 3). Drugs were diluted with 0.9% saline to obtain the respective doses (clozapine was previously diluted

TABLE 1

MEAN NUMBER (±STANDARD ERROR) OF AVOIDANCES, ESCAPES, NONRESPONSES, CROSSINGS DURING THE ADAPTATION PERIOD (ADAP-CROSS), AND CROSSINGS DURING ITIs (ITI-CROSS); AND MEAN LATENCIES OF RESPONSES AFTER ACUTE ADMINISTRATION OF RACLOPRIDE (EXPERIMENT 1)

	Avoidances	Escapes	Nonresp.	Latencies	Adap-Cross	ITI-Cross
			Treatment			
Saline	1.8 ± 0.6	27.05 ± 0.8	1.15 ± 0.4	6.65 ± 0.2	14.3 ± 1.3	13.19 ± 4.5
Raclopride 0.4 mg/kg	0.7 ± 0.3*	21.7 ± 1.6*	7.6 ± 1.7†	7.87 ± 0.3†	10.25 ± 1.2*	5.85 ± 1.0*
Raclopride 1.2 mg/kg	0.5 ± 0.2*	17.55 ± 1.8†	11.95 ± 1.8†	8.23 ± 0.2†	7.45 ± 1.2*	5.35 ± 1.2*
Raclopride 3.6 mg/kg	0.35 ± 0.2*	12.05 ± 2.2†	12.6 ± 2.3†	8.88 ± 0.4†	5.15 ± 1.1†	2.2 ± 0.4†
	$p < 0.05$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.01$
			Sex Differences			
Saline						
Males	2.4 ± 1.1	26.2 ± 1.2	1.4 ± 0.6	6.76 ± 0.34	14.1 ± 1.51	14.1 ± 6.42
Females	1.2 ± 0.5	27.9 ± 1.0	0.9 ± 0.54	6.53 ± 0.17	14.5 ± 2.37	13.7 ± 6.72
	NS	NS	NS	NS	NS	NS
Raclopride 0.4 mg/kg						
Males	0.9 ± 0.23	21.2 ± 2.47	7.9 ± 2.48	8.03 ± 0.43	8.8 ± 1.86	5.6 ± 1.4
Females	0.5 ± 0.50	22.2 ± 2.26	7.3 ± 2.38	7.72 ± 0.29	11.7 ± 1.58	6.1 ± 1.66
	NS	NS	NS	NS	NS	NS
Raclopride 1.2 mg/kg						
Males	0.7 ± 0.33	17.7 ± 2.12	11.6 ± 2.15	8.52 ± 0.31	6.0 ± 1.35	7.1 ± 2.18
Females	0.3 ± 0.15	17.4 ± 3.14	12.3 ± 3.07	7.93 ± 0.30	8.9 ± 1.97	3.6 ± 1.01
	NS	NS	NS	NS	NS	NS
Raclopride 3.6 mg/kg						
Males	0.5 ± 0.27	7.8 ± 2.99	21.7 ± 3.19	9.31 ± 0.90	6.0 ± 1.84	2.3 ± 0.67
Females	0.2 ± 0.20	16.3 ± 2.78	13.5 ± 2.86	8.44 ± 0.36	4.3 ± 1.41	2.1 ± 0.46
	NS	$p < 0.05$	$p < 0.05$	NS	NS	NS

*$p < 0.05$ and †$p < 0.01$ vs. saline group (Newman–Keuls).

with a drop of HCl, 0.1 N). Controls received 0.9% saline alone. Injections were administered IP in a volume of 0.01 ml/g body weight.

Apparatus

Two computerized two-way shuttle-boxes (Shuttle Scan, Model SC-II, Omnitech Electronics, Inc., Columbus, OH) described in detail elsewhere (3), and RMS V.2.06 Omnitech Electronics software were used. Each shuttle-box was located in an insulating box.

Procedure

After the period of adaptation to the laboratory, the animals were randomly assigned to one of four groups ($n = 10$) in each sex and received 0.9% saline or one of the three doses of the respective drug. Each animal was tested once in the shuttle-box 30 min after injection. The test consisted of (a) 2 min of adaptation to the apparatus, in which the animal explored the box and moved freely; (b) 30 trials of two-way escape–avoidance with an intertrial interval (ITI) of 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 with 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 light period only; an escape was defined as a crossing when the shock was on; and a nonresponse was defined as the absence of crossing. All tests were run between 0900 and 1600 h (local time). The following behavioral parameters were computed: number of avoidances, number of escapes, number of nonresponses, response latencies (avoidances and escapes), number of crossings during the adaptation period, and number of crossings during ITIs.

Statistical Analysis

All measures were subjected to analysis of variance (ANOVA) in each experiment, with treatment and sex as the main factors, supplemented by Newman–Keuls pairwise comparisons and tests of simple main effects. The best-fit quadratic function was calculated to study the relationship between the doses of each drug and the sex differences found in the number of escapes and the number of nonresponses, as in a previous study (43).

RESULTS

Experiment 1: Raclopride

Table 1 summarizes the effects of raclopride on the different variables of the escape–avoidance response and the sex differences found in these effects. All the tested doses effectively decreased the number of avoidances, $F(3, 72) = 3.46$, $p < 0.05$, (Newman–Keuls: $p < 0.05$, all cases), as well as the number of escapes, $F(3, 72) = 14.41$, $p < 0.0001$, in the animals treated with 0.4 mg/kg (Newman–Keuls: $p < 0.05$), and also those treated with 1.2 or 3.6 mg/kg of raclopride (Newman–Keuls: $p < 0.01$, both cases). The number of nonresponses increased, $F(3, 72) = 17.17$, $p < 0.0001$, with all of the doses (Newman–Keuls: $p < 0.01$, all cases), and the drug also significantly increased response latencies, $F(3, 69) = 11.27$, $p < 0.0001$, with all the animals treated with raclopride showing longer latencies than the saline controls (Newman–Keuls: $p < 0.01$, all cases).

Regarding the spontaneous motor activity measures, the number of crossings during the adaptation period, $F(3, 72) = 9.93$, $p < 0.0001$, as well as the number of crossings during ITIs, $F(3, 72) = 4.08$, $p < 0.01$, were significantly decreased by treatment. Raclopride reduced both crossings in the 0.4 and 1.2 mg/kg groups (Newman–Keuls: $p < 0.05$) and in the 3.6 mg/kg group (Newman–Keuls: $p < 0.01$).

The simple main effects analysis showed that raclopride significantly reduced the number of avoidances in males, $F(3, 72) = 3.002$, $p < 0.05$, but not in females, $F(3, 72) = 0.815$, NS. The simple main effects analysis also revealed sex differences in the groups treated with the highest dose of raclopride in the number of escapes, $F(1, 72) = 6.45$, $p < 0.05$, with males showing fewer escapes than females; as well as in the number of nonresponses, $F(1, 72) = 5.97$, $p < 0.05$, where the male group of 3.6 mg/kg of raclopride had more nonresponses than its respective female group. No sex differences were found with the rest of the treatments.

The relationship between the doses of raclopride and the sex differences found in the number of escapes and the number of nonresponses was determined to check if the sex differences were dose dependent. A positive correlation was found between the doses of raclopride and the sex differences observed in the number of escapes (mean of escapes in females minus mean of escapes in males) ($r^2 = 0.997$) and the number of nonresponses (mean of nonresponses in males minus mean of nonresponses in females) ($r^2 = 0.989$); the higher the dose, the greater the sex differences (see Fig. 1).

No sex differences were observed in either of the motor activity measures: the number of crossings during the adapta-

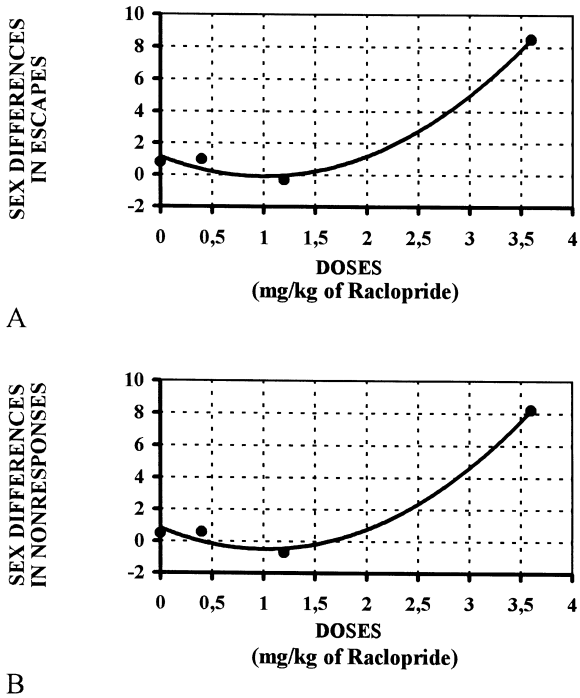


FIG. 1 Relationship between doses of raclopride and sex differences in: (A) escapes (mean number of escapes in females minus mean number of escapes in males), the best-fit quadratic function fitted to the data is based on the equation $y = 1.4754\ x^2 - 3.4722\ x + 1.8685$ ($r^2 = 0.997$); and (B) nonresponses (mean number of nonresponses in males minus mean number of nonresponses in females), $y = 1.2952\ x^2 - 2.6274\ x + 0.85115$ ($r^2 = 0.989$).

tion period, $F(1, 72) = 0.81$, NS, and the number of crossings during ITIs, $F(1, 72) = 0.13$, NS.

Experiment 2: Clozapine

Table 2 summarizes the effects of clozapine on the different variables of the escape–avoidance response and the sex differences found in these effects. This neuroleptic decreased the number of escapes, $F(3, 72) = 3.88$, $p < 0.05$, with the animals treated with 3 or 9 mg/kg of clozapine showing less escapes than the control animals (Newman–Keuls: $p < 0.05$, both cases); and increased the number of nonresponses, $F(3, 72) = 4.58$, $p < 0.005$, specifically in the animals treated with 9 mg/kg of clozapine (Newman–Keuls: $p < 0.01$). Clozapine also significantly increased response latencies, $F(3, 72) = 32.75$, $p < 0.0001$, with the animals treated with 3 mg/kg (Newman–Keuls: $p < 0.05$) or 9 mg/kg of clozapine (Newman–Keuls: $p < 0.01$), showing longer latencies than saline controls. Treatment was also statistically significant in the number of crossings during the adaptation period, $F(3, 72) = 13.16$, $p < 0.0001$. Clozapine reduced these crossings in the subjects treated with 3 and 9 mg/kg (Newman–Keuls: $p < 0.01$, both cases).

Sex differences were observed in the number of escapes. The main factor sex was statistically significant, with males showing less escapes than females, $F(1, 72) = 4.15$, $p < 0.05$. The males treated with 3 mg/kg, $F(1, 72) = 4.71$, $p < 0.05$, and 9 mg/kg of clozapine, $F(1, 72) = 5.32$, $p < 0.05$, made less escapes than their respective females. There were also sex differences in the number of nonresponses: males had more nonresponses than females in the groups treated with 9 mg/kg of clozapine, $F(1, 72) = 4.44$, $p < 0.05$. The simple main effects analysis also revealed that clozapine reduced the number of escapes in males, $F(3, 72) = 5.16$, $p < 0.005$, but not in females, $F(3, 72) = 0.86$, NS; and in a similar way, the antipsychotic increased the number of nonresponses in males, $F(3, 72) = 6.26$, $p < 0.001$, but not in females, $F(3, 72) = 0.45$, NS.

The relationship between the doses of clozapine and the sex differences found in the number of escapes and the number of nonresponses was also determined. As in Experiment 1, a positive correlation was obtained between the doses of clozapine and the sex differences observed in the number of escapes ($r^2 = 0.703$) and the number of nonresponses ($r^2 = 0.82$) (see Fig. 2).

Sex was statistically significant in the number of crossings during ITIs as well, with males showing a higher number of these crossings than females, $F(1, 72) = 4.02$, $p < 0.05$. Specifically, sex differences were observed with 3 mg/kg of clozapine, $F(1, 72) = 3.75$, $p = 0.05$.

Experiment 3: SCH 23390

Table 3 summarizes the effects of SCH 23390 on the different variables of the escape–avoidance response and the sex differences found in these effects. All the SCH 23390 doses significantly decreased the number of avoidances, $F(3, 72) = 9.01$, $p < 0.0001$ (Newman–Keuls: $p < 0.01$, all cases). This drug also reduced the number of escapes, $F(3, 72) = 5.45$, $p < 0.005$. The animals treated with 0.06 mg/kg (Newman–Keuls: $p < 0.05$) and those treated with 0.2 mg/kg or 0.6 mg/kg of SCH 23390 (Newman–Keuls: $p < 0.01$, both cases) had less escapes than the animals treated with saline. The number of

TABLE 2

MEAN NUMBER (±STANDARD ERROR) OF AVOIDANCES, ESCAPES, NONRESPONSES, CROSSINGS DURING THE ADAPTATION PERIOD (ADAP-CROSS), AND CROSSINGS DURING ITIs (ITI-CROSS); AND MEAN LATENCIES OF RESPONSES AFTER ACUTE ADMINISTRATION OF CLOZAPINE (EXPERIMENT 2)

	Avoidances	Escapes	Nonresp.	Latencies	Adap-Cross	ITI-Cross
			Treatment			
Saline	1.05 ± 0.3	28.2 ± 0.4	0.75 ± 0.3	6.58 ± 0.2	14.35 ± 1.3	12.05 ± 2.4
Clozapine 1 mg/kg	2.4 ± 0.7	25.85 ± 1.0	1.75 ± 0.6	6.56 ± 0.2	12.4 ± 1.2	16.1 ± 4.3
Clozapine 3 mg/kg	1.8 ± 0.5	24 ± 1.5*	4.2 ± 1.5	7.45 ± 0.3*	6.05 ± 1.2†	14.75 ± 4.4
Clozapine 9 mg/kg	0.75 ± 0.3	23.35 ± 1.4*	5.9 ± 1.5†	9.24 ± 0.2†	4.15 ± 1.5†	6.55 ± 1.6
	NS	$p < 0.05$	$p < 0.005$	$p < 0.0001$	$p < 0.0001$	NS
			Sex Differences			
Saline						
Males	1.7 ± 0.39	27.9 ± 0.43	0.4 ± 0.16	6.39 ± 0.17	13.9 ± 1.55	16.6 ± 4.09
Females	0.4 ± 0.30	28.5 ± 0.65	1.1 ± 0.65	6.77 ± 0.26	14.8 ± 2.15	7.5 ± 1.82
	NS	NS	NS	NS	NS	NS
Clozapine 1 mg/kg						
Males	2.6 ± 0.98	26.6 ± 1.02	0.8 ± 0.44	6.64 ± 0.32	12.2 ± 1.08	18.3 ± 6.12
Females	2.2 ± 1.03	25.1 ± 1.73	2.7 ± 1.01	6.48 ± 0.27	12.6 ± 2.23	13.9 ± 6.48
	NS	NS	NS	NS	NS	NS
Clozapine 3 mg/kg						
Males	2.4 ± 0.92	21.6 ± 2.44	6.0 ± 2.62	7.70 ± 0.42	6.0 ± 2.06	21.3 ± 8.17
Females	1.2 ± 0.57	26.4 ± 1.45	2.4 ± 1.51	7.20 ± 0.36	6.1 ± 1.48	8.2 ± 2.35
	NS	$p < 0.05$	NS	NS	NS	$p = 0.05$
Clozapine 9 mg/kg						
Males	1.0 ± 0.63	20.8 ± 2.27	8.2 ± 2.55	9.66 ± 0.35	3.5 ± 1.96	6.8 ± 2.81
Females	0.5 ± 0.31	25.9 ± 1.27	3.6 ± 1.31	8.82 ± 0.25	4.8 ± 2.41	6.3 ± 1.72
	NS	$p < 0.05$	$p < 0.05$	NS	NS	NS

*$p < 0.05$ and †$p < 0.01$ vs. saline group (Newman–Keuls).

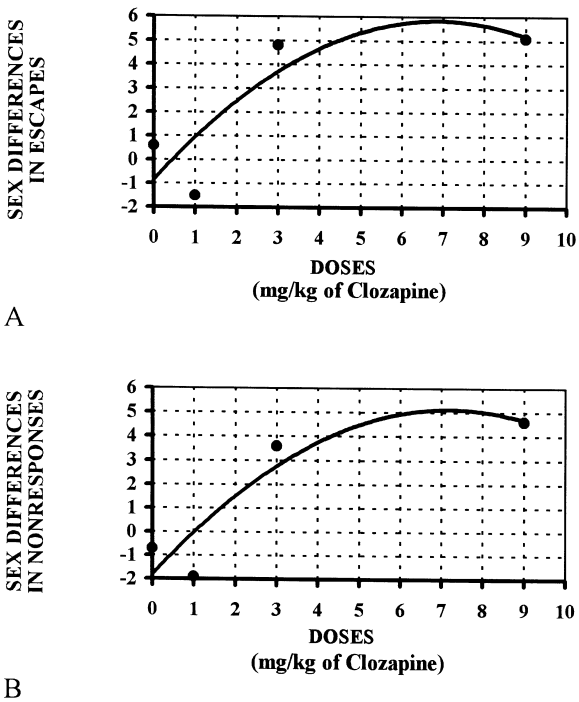


FIG. 2. Relationship between doses of clozapine and sex differences in: (A) escapes (mean number of escapes in females minus mean number of escapes in males), the best-fit quadratic function fitted to the data is based on the equation $y = -7.14159\ x^2 + 1.9458\ x - 0.85274$ ($r^2 = 0.703$); and (B) nonresponses (mean number of nonresponses in males minus mean number of nonresponses in females), $y = -0.13429\ x^2 + 1.9291\ x - 1.8143$ ($r^2 = 0.82$).

nonresponses increased, $F(3, 72) = 8.67$, $p < 0.0001$, with all the doses (Newman–Keuls: $p < 0.01$, all cases); as did response latencies, $F(3, 72) = 6.02$, $p < 0.001$, with all the animals treated with SCH 23390 showing longer latencies than the saline controls (Newman–Keuls: $p < 0.01$, all cases).

Treatment was also statistically significant in the number of crossings during the adaptation period, $F(3, 72) = 7.95$, $p < 0.0001$, and crossings during ITIs, $F(3, 72) = 3.72$, $p < 0.05$. SCH 23390 reduced the adaptation crossings in the 0.06 mg/kg group (Newman–Keuls: $p < 0.05$) and in the 0.2 or 0.6 mg/kg groups (Newman–Keuls: $p < 0.01$, both cases), while ITIs crossings were reduced in the 0.6 mg/kg group (Newman–Keuls: $p < 0.01$).

The simple main effects analysis showed that SCH 23390 significantly decreased the number of avoidances in males, $F(3, 72) = 6.29$, $p < 0.001$, but not in females, $F(3, 72) = 2.57$, NS.

Sex was statistically significant in the number of escapes, $F(1, 72) = 20.72$, $p < 0.0001$; males showed less escapes than females. Specifically, males treated with 0.06 mg/kg, $F(1, 72) = 12.55$, $p < 0.001$, or 0.6 mg/kg of SCH 23390, $F(1, 72) = 11.40$, $p < 0.001$, had less escapes than their respective females. Factor sex was also significant in the number of nonresponses, $F(1, 72) = 19.15$, $p < 0.0001$; males had more nonresponses than females in the groups treated with 0.06 mg/kg, $F(1, 72) = 13.79$, $p < 0.0001$, and 0.6 mg/kg of SCH 23390, $F(1, 72) = 10.56$, $p < 0.005$. The simple main effects analysis also revealed that SCH 23390 reduced the number of escapes in males, $F(3, 72) = 5.61$, $p < 0.005$, but not in females, $F(3,72) = 1.87$, NS; and similarly, the drug increased the number of nonresponses in males, $F(3, 72) = 8.5$, $p < 0.0001$, but not in females, $F(3, 72) = 2.69$, NS.

As in the two previous experiments, the relationship between the doses of SCH 23390 and the sex differences found in the number of escapes and the number of nonresponses was determined. A positive but low correlation was obtained between the doses of SCH 23390 and the sex differences observed in the number of escapes ($r^2 = 0.269$) and the number of nonresponses ($r^2 = 0.219$) (see Fig. 3).

There were also sex differences in the number of crossings during the adaptation period, $F(1, 72) = 4.08$, $p < 0.05$, where males showed fewer crossings than females in the animals treated with saline, $F(1, 72) = 4.08$, $p < 0.05$. No sex differences were observed in the number of crossings during ITIs.

DISCUSSION

The effects of three dopamine antagonists (raclopride, clozapine, and SCH 23390) on several parameters of the escape–avoidance response in OF1 mice were evaluated in the present study. Three doses of each compound were used in acute administration in a unique training session (30 trials) in separate experiments. It could be argued that several sessions are necessary to properly study the sex differences in the effects of these drugs in escape–avoidance response, but we have previously found these sex differences just in one session (3,4,42,43). Also, it is important to note that the doses employed in this study are too high for repeated administration.

The drugs evaluated significantly decreased the number of avoidances (with the exception of clozapine) and the number of escapes; and they increased response latencies and the number of nonresponses. All three drugs also diminished the spontaneous motor activity by decreasing the number of crossings during the adaptation period and intertrial intervals. Thus, it cannot be excluded that the present effects on avoidance–escape responding are mainly due to motor impairing effects.

In the present study, the inhibitory effect of the selective D_2 dopamine receptor antagonist raclopride was stronger in males than in females. This antipsychotic reduced the number of avoidances in males but not in females, and statistically significant sex differences were found in the number of escapes and nonresponses, with males showing less escapes and more nonresponses than females with the dose of 3.6 mg/kg of raclopride.

Clozapine, a nonselective dopamine receptor antagonist, showed similar sex differences in its effects in the escape–avoidance response. The doses of 3.0 mg/kg and 9.0 mg/kg diminished the number of escapes more in males than in females, and the dose 9.0 mg/kg of clozapine increased the number of nonresponses more in male mice. Another sex difference was observed in the number of crossings during ITIs: males treated with 3.0 mg/kg of clozapine had a higher number of these crossings than their respective females.

The specific D_1 dopamine receptor antagonist SCH 23390 also produced different effects in each sex. SCH 23390 decreased the number of escapes and increased the number of nonresponses in males but not in females. Specifically, the doses of 0.06 mg/kg and 0.6 mg/kg of SCH 23390 reduced the number of escapes and increased the number of nonresponses more in males than in females. And males had less crossings during the adaptation period than females in the control groups treated with saline.

Thus, the present results confirm the sex differences observed in the effects of neuroleptics in several experimental

TABLE 3

MEAN NUMBER (±STANDARD ERROR) OF AVOIDANCES, ESCAPES, NONRESPONSES, CROSSINGS DURING THE ADAPTATION PERIOD (ADAP-CROSS), AND CROSSINGS DURING ITIs (ITI-CROSS); AND MEAN LATENCIES OF RESPONSES AFTER ACUTE ADMINISTRATION OF SCH 23390 (EXPERIMENT 3)

	Avoidances	Escapes	Nonresp.	Latencies	Adap-Cross	ITI-Cross
			Treatment			
Saline	2.5 ± 0.5	26.1 ± 0.6	1.4 ± 0.4	6.76 ± 0.2	13.65 ± 1.4	15.65 ± 3.2
SCH 23390-0.06 mg/kg	0.75 ± 0.2†	21.35 ± 2.0*	7.9 ± 2.0†	7.87 ± 0.3†	8.8 ± 1.3*	9.2 ± 1.9
SCH 23390-0.2 mg/kg	0.6 ± 0.2†	18.3 ± 1.8†	11.1 ± 1.8†	7.83 ± 0.2†	7.6 ± 1.3†	9.25 ± 1.8
SCH 23390-0.6 mg/kg	0.5 ± 0.1†	19 ± 2.1†	10.5 ± 2.0†	8.04 ± 0.3†	4.95 ± 1.0†	5.35 ± 1.4†
	$p < 0.0001$	$p < 0.005$	$p < 0.0001$	$p < 0.001$	$p < 0.0001$	$p < 0.05$
			Sex Differences			
Saline						
Males	3.0 ± 1.01	25.2 ± 0.95	1.8 ± 0.78	7.15 ± 0.38	10.7 ± 1.59	13.5 ± 4.15
Females	2.0 ± 0.55	27.0 ± 0.71	1.0 ± 0.47	6.37 ± 0.11	15.6 ± 2.00	17.8 ± 4.91
	NS	NS	NS	NS	$p < 0.05$	NS
SCH 23390—0.06 mg/kg						
Males	0.5 ± 0.27	16.0 ± 3.07	13.5 ± 3.05	8.29 ± 0.46	7.0 ± 1.78	7.9 ± 3.04
Females	1.0 ± 0.33	26.7 ± 0.88	2.3 ± 0.82	7.44 ± 0.43	10.6 ± 1.71	10.5 ± 2.58
	NS	$p < 0.001$	$p < 0.0001$	NS	NS	NS
SCH 23390—0.2 mg/kg						
Males	0.7 ± 0.33	15.9 ± 2.09	13.4 ± 2.13	8.37 ± 0.27	6.8 ± 1.44	11.2 ± 2.57
Females	0.5 ± 0.27	20.7 ± 2.83	8.8 ± 2.91	7.28 ± 0.15	8.4 ± 2.16	7.3 ± 2.61
	NS	NS	NS	NS	NS	NS
SCH 23390—0.6 mg/kg						
Males	0.7 ± 0.26	13.9 ± 2.80	15.4 ± 2.87	8.54 ± 0.41	5.1 ± 1.68	6.3 ± 2.15
Females	0.3 ± 0.15	24.1 ± 2.13	5.6 ± 2.07	7.54 ± 0.29	4.8 ± 1.13	4.4 ± 1.74
	NS	$p < 0.001$	$p < 0.005$	NS	NS	NS

*$p < 0.05$ and †$p < 0.01$ vs. saline group (Newman–Keuls).

procedures with animals (3,4,6,11,15,19,34,42,43,45,53) as well as with human subjects (18,31,37,41,55,57–59,61,62,67).

A positive correlation was obtained between the doses of each drug and the sex differences observed in the number of escapes and nonresponses. In general, the higher the dose, the greater the sex differences. This indicates that the sex differences in the effects of dopamine antagonists in escape–avoidance response in mice is a dose-dependent phenomenon.

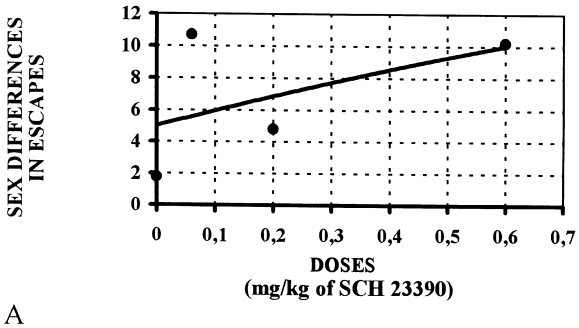
Considering the relationship between sex and dose, the most important statistical result would be a significant interaction between them. Such interaction did not reach a statistically significant level in any of the drugs. This could be due to the fact that the drug effects are inhibitory in both sexes. This is a matter of degree in the same direction of the effects.

These sex differences are not only related to the impairment of motor activity but also to the very learning process taking into account the results obtained in the number of crossings during the adaptation period and crossings during intertrial intervals, both measures of the animals' spontaneous motor activity. No sex differences were found in these measures with raclopride. Even though there were sex differences in the effect of clozapine in the number of crossings during ITIs, it must be noted that males had more crossings than females (indicator of more activity), which is in the opposite direction of the sex differences observed in the measures of conditioning, where performance deteriorated in males more than in females. And although there were also sex differences in the effect of SCH 23390 in the number of crossings during the adaptation period, they were not found in the experimental groups but rather with the control animals treated with saline. Therefore, the sex differences observed in the effects of dopamine antagonists in escape–avoidance response are not purely due to a differential impairment of motor behavior but they are related to the very learning process.

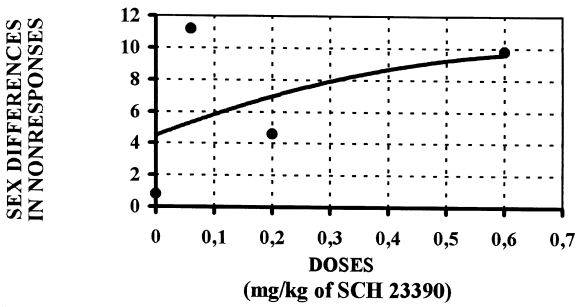
The three drugs used in the present study have different affinities for D_1 and D_2 dopaminergic receptors: raclopride, a highly selective D_2 dopamine receptor antagonist (24,25,44); clozapine, a nonselective antagonist with comparable D_1–D_2 affinities (10,16,25,26,50,51); and SCH 23390, a specific D_1 dopamine receptor antagonist (35,36). Sex differences were found with all of the three dopamine antagonists studied, indicating, therefore, that these differences do not depend on a unique type of dopaminergic receptor.

Several explanations for the origin of the sex differences observed in the action of neuroleptics have been proposed. It could be considered that female mice are more sensitive to pain and react more quickly to shock presentation than males. If so, there ought to be sex differences in saline subjects; however, these differences were only found in drug-treated animals in the present study and similar previous studies (3,4,43). To accept this interpretation of the facts, it would be necessary to admit that neuroleptics attenuate sensitivity to shock in both sexes, and that this decrement is greater in males than in females.

Numerous studies also suggest that central dopaminergic transmission is modulated by estrogens (8,20–23,29,30,39,48, 60,67). Thus, the acquisition of conditioned avoidance responses is influenced by the sexual hormone changes that occur during the rat's estrous cycle (20–22). An important hypothesis postulates antidopaminergic properties of estrogens



A



B

FIG. 3. Relationship between doses of SCH 23390 and sex differences in: (A) escapes (mean number of escapes in females minus mean number of escapes in males), the best-fit quadratic function fitted to the data is based on the equation $y = -2.2872\,x^2 + 9.7113\,x + 5.0179$ ($r^2 = 0.269$); and (B) nonresponses (mean number of nonresponses in males minus mean number of nonresponses in females), $y = -9.7553\,x^2 + 14.343\,x + 4.5006$ ($r^2 = 0.219$).

as a protective function in schizophrenia. This hypothesis accounts for many of the observed gender differences, such as a later onset of illness, better outcome indices and superior neuroleptic response in women, as well as an exacerbation of symptoms in periods of low levels of estrogens, for example, after menopause (60).

Finally, pharmacokinetic differences between male and female schizophrenic patients have been observed. Women with chronic schizophrenia have been reported to have both higher prolactin and HVA levels than men while taking neuroleptics (61,67). The pharmacokinetic differences could be due to differences in absorption because gastric acid secretion differs between men and women. Gastric emptying and also gastrointestinal transit time is slower in females than in males and appears to be correlated with the level of sex hormones (28). With respect to distribution, lipid-soluble neuroleptics are distributed comparatively widely and show longer elimination half-lives in women because they have a higher proportion of adipose tissue than men (18,59). Another possible explanation refers to different intensities of hepatic catabolism of neuroleptics in males and females. Liver enzymatic activity is generally thought to be more efficient in men (59). This fact would not explain neither the present results nor previous studies (3,4,42,43), where males were more affected than females by haloperidol.

Therefore, the neurochemical mechanisms involved in the origin of the sex differences in the effects of neuroleptics in escape–avoidance response in mice remains unclear, and further investigation is required in this area.

We may conclude that other dopaminergic antagonists besides haloperidol show sex differences in their behavioral effects in the escape–avoidance response in mice, with males being more affected than females by the inhibitory action of these drugs. These sex differences in the escape–avoidance response were dose dependent: the higher the dose; the greater the sex differences.

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