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The Higher the Dose, the Greater the Sex Differences in Escape–Avoidance Response in Mice After Acute Administration of Haloperidol

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MONLEÓN, S. AND A. PARRA. *The higher the dose, the greater the sex differences in escape–avoidance response in mice after acute administration of haloperidol.* PHARMACOL BIOCHEM BEHAV **60**(1) 279–284, 1998.—Sex differences in the effects of haloperidol in the escape–avoidance response have previously been found in various studies carried out in our laboratory in which mice were used as experimental subjects. Males were more affected than females by the disruptive effects of this neuroleptic of frequent clinical use. In the present work these sex differences were evaluated in a unique training session using several doses of the drug (0.075, 0.25, and 0.75 mg/kg IP). The number of avoidances, escapes, nonresponses, crossings during the adaptation period, crossings during intertrial intervals, and response latencies were analyzed. Statistically significant sex differences were found in the number of escapes and nonresponses: males showed fewer escape responses and more nonresponses than females. These sex differences were dose dependent: a positive correlation was obtained between doses of haloperidol and sex differences observed in the number of escapes and nonresponses. The higher the dose, the greater the sex differences. These are related not only to the impairment of motor activity, because no sex differences were found in the number of crossings during the adaptation period and intertrial intervals. © 1998 Elsevier Sciences Inc.

Sex differences Active avoidance Learning Neuroleptics Haloperidol Mice

ESCAPE–AVOIDANCE response has been considered a useful tool for selecting and studying antipsychotic drugs (14,16, 18,31,47); such drugs disrupt the ability of animals to avoid shock at doses that do no alter escape behavior (14,39,42,56). Many studies have shown that haloperidol, like other neuroleptics, produces a dose-dependent impairment on the acquisition and performance of this active avoidance conditioning. These effects of haloperidol on acquisition of a conditioned avoidance response in rodents have been explored in studies using acute administration (3,4,18,33,44,46,47,50,52,54,64,65,66) and studies in which haloperidol was repeatedly administered (5,6,9,13,30,56).

Also sex differences in the effects of haloperidol (and other neuroleptics) have been described in human subjects (19,28,36,43,55,57–59,61,62,68) as well as in several experimental procedures with animals (4,5,7,8,12,17,20,32,44,45,53).

Sex differences in the effects of haloperidol on escape–avoidance response have previously been found in several studies carried out in our laboratory using mice as experimental subjects (4,5,44).

In one study, sex differences in the effects of haloperidol were observed in the unique training session of an active avoidance task. Using a dose (0.25 mg/kg) that clearly deteriorates avoidance responses in rats (56), OF1 male mice showed fewer escape responses and more nonresponses than females; however, sex differences were not observed in motor activity, measured by the number of crossings during the adaptation period and intertrial intervals (4). Similar results have recently been found with BALB/c mice (44).

Another study (5) was carried out to further evaluate sex differences in acquisition and performance of escape–avoidance response in mice. The drug's effects on motor behavior were also controlled. 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, 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

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found after this lapse of time (2,41). 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 (5).

The present investigation was designed to evaluate the sex differences in the effects of several doses of haloperidol (0.075, 0.25, and 0.75 mg/kg) on escape–avoidance response in OF1 mice after a single administration.

METHOD

Subjects

Forty male and 40 female OF1 mice from IFFA CREDO (Lyon, France), weighing between 30–36 g and 24–28 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 in the same room, for 13 days, in unisexual groups of five in translucent plastic cages ($25 \times 25 \times 14.5$ cm) under a reversed light–dark cycle (lights off: 0630–1830 hours, local time) with food and water available ad lib, and controlled room temperature (22 ± 2°C).

Drugs

Haloperidol (Haloperidol®, Syntex Latino, Spain) was diluted with 0.9% saline to obtain the doses of 0.075, 0.25, and 0.75 mg/kg. Control animals received 0.9% saline alone. Injections were administered intraperitoneally (IP) in a volume of 0.01 ml/g body weight.

Apparatus

A computerized two-way shuttle-box (Shuttle Scan, Model SC-II, Omnitech Electronics, Inc., Columbus, OH) described in detail elsewhere (4), and the RMS V.2.06 Omnitech Electronics software were used.

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 the following treatments: (a) 0.9% saline, (b) 0.075 mg/kg of haloperidol, (c) 0.25 mg/kg of haloperidol, or (d) 0.75 mg/kg of haloperidol. Each animal was tested once in the shuttle-box 30 min after injection. This pretreatment time was selected given that maximal brain concentrations of haloperidol in mice are attained 15 min after injection and remain high, although slowly declining, for 2 h after injection (69). Also, this pretreatment interval allows testing animals in a successive sequence and timely fashion. The test consisted of: (a) 2 min of adaptation to the apparatus, in which the animal explored the box and moved freely; and (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. A conditioned avoidance response was defined as a crossing to the opposite side during only the light period; 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 in a room different from the home room between 0900 and 1600 h (local time).

The following behavioral parameters were computed: number of avoidances, number of escapes, number of nonresponses, latencies of responses (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), with treatment and sex as the main factors, supplemented by Newman–Keuls pairwise comparisons and tests of simple main effects.

RESULTS

Table 1 summarizes the effects of haloperidol on the different variables of the escape–avoidance response and the sex differences found in these effects. The drug decreased the number of escapes, $F(3, 72) = 13.92$, $p < 0.0001$, and increased the number of nonresponses, $F(3, 72) = 15.87$, $p < 0.0001$; the animals treated with 0.25 mg/kg or 0.75 mg/kg of haloperidol had less escapes and more nonresponses than the animals treated with saline (Newman–Keuls: $p < 0.01$, in all cases). Haloperidol also significantly increased response latencies, $F(3, 72) = 13.13$, $p < 0.0001$. The animals treated with 0.075 mg/kg (Newman–Keuls: $p < 0.05$) as well as those treated with 0.25 mg/kg or 0.75 mg/kg of haloperidol showed longer latencies than the saline controls (Neuman–Keuls: $p < 0.01$, both cases). Treatment was also statistically significant in the number of crossings during the adaptation period, $F(3, 72) = 4.49$; $p < 0.01$ and crossings during ITIs, $F(3,72) = 4.64$; $p = 0.005$; haloperidol reduced the crossings during the adaptation period of the 0.75 mg/kg group (Newman–Keuls: $p < 0.01$) and the ITIs crossings of the 0.25 mg/kg and 0.75 mg/kg groups (Newman–Keuls: $p < 0.01$, both cases).

Regarding the number of avoidances, the test of simple main effects showed sex differences in the control groups treated with saline, $F(1, 72) = 4.23$, $p < 0.05$: males showed a higher number of avoidances. And although treatment was not significant in this measure, $F(3, 72) = 1.85$, NS, the simple main effects analysis also revealed that haloperidol reduced the number of avoidances in males, $F(3, 72) = 2.91$, $p < 0.05$, but not in females, $F(3, 72) = 0.48$, NS.

The factor sex was statistically significant in the number of escapes, $F(1, 72) = 4.27$, $p < 0.05$, with females showing more escapes than males. The simple main effects analysis revealed sex differences in the animals treated with 0.75 mg/kg of haloperidol, $F(1, 72) = 5.24$, $p < 0.05$, with females having more escapes than males. No sex differences were found in the rest of treatments.

There were also significant sex differences in the number of nonresponses, with males showing a higher number of nonresponses than females, $F(1, 72) = 3.96$, $p = 0.05$. The simple main effects analysis revealed sex differences in the animals treated with 0.75 mg/kg of haloperidol, $F(1, 72) = 5.65$, $p < 0.05$. Moreover, the male groups of 0.25 mg/kg or 0.75 mg/kg showed more nonresponses than the control group (Newman–Keuls: $p < 0.01$), while with the females only one group (0.25 mg/kg) was statistically different from the saline group ($p < 0.05$).

An interesting point to investigate is the existence of a dose-dependent relationship between the doses of haloperidol and the sex differences observed in the number of escapes and the number of nonresponses. These measures were selected because they have usually been revealed to be the most sensitive for showing sex differences in the effects of haloperidol on the escape–avoidance response (4,5). A positive correlation was found between the doses of haloperidol and the sex differences observed in the number of escapes (mean of es-

capes in females minus mean of escapes in males) ($r^2 = 0.938$) and the number of nonresponses (mean of nonresponses in males minus mean of nonresponses in females) ($r^2 = 0.897$); the higher the dose, the greater the sex differences (see Fig. 1).

Sex was nearly statistically significant in response latencies, $F(1,72) = 3.74$, $p = 0.057$, indicating longer latencies of responses in males. And the test of simple main effects showed sex differences with the 0.25 mg/kg dose of haloperidol, $F(1, 72) = 4.11$, $p < 0.05$. Furthermore, males treated with 0.25 mg/kg or 0.75 mg/kg of haloperidol had longer latencies than saline males (Newman–Keuls: $p < 0.01$), while with the females only the 0.75 mg/kg group showed longer latencies than the saline group (Newman–Keuls: $p < 0.05$).

No sex differences were observed in the motor activity measures in either the number of crossings during the adaptation period or crossings during ITIs, Fs < 1; NS.

DISCUSSION

The effects of three doses (0.075, 0.25, and 0.75 mg/kg IP) of haloperidol on several parameters of the escape–avoidance response in OF1 mice were evaluated. The results obtained are a further example of the well-known inhibitory effect of this drug on conditioned avoidance response, showing a decrease in the number of escapes and an increase in response latencies and the number of nonresponses. Haloperidol also diminished the spontaneous motor activity by decreasing the number of crossings during the adaptation period and intertrial intervals.

Neuroleptics have the specific effect on conditioned avoidance response (CAR) of reducing the number of avoidances and increasing the number of escapes without affecting the number of nonresponses [e.g. (14)]. This result is obtained when low doses and several sessions are involved. In the present experiment, haloperidol doses of 0.25 and 0.75 mg/kg (which are higher than those used in CAR experiments) reduced the number of escapes and increased the number of nonresponses. This could be considered as a nonspecific effect.

The inhibitory effect of haloperidol was stronger on males than females. Significant sex differences were found in the number of escapes and nonresponses, with males showing less escapes and more nonresponses than females. Sex differences were statistically significant at the highest dose (0.75 mg/kg) of haloperidol.

There were also specific sex differences in response latencies, where males treated with 0.25 mg/kg of haloperidol had longer latencies than their respective females; and in the number of avoidances, where males had more avoidances than females in the saline groups. The difference in avoidance has to be considered with caution due to the low number of avoidances (the average in the most favorable case—saline males—is of 1.5 avoidances per animal). Avoidances in only one session of escape–avoidance are not a relevant parameter.

It can be argued that the sex differences observed at the highest dose were secondary to sex differences in the cataleptogenic effects of haloperidol. Our results in the spontaneous motor activity measures did not show sex differences. Nor does literature data support such an assumption because the haloperidol made the male mice less cataleptic than females (45).

A positive correlation was obtained between doses of haloperidol and sex differences found in the number of escapes and nonresponses. The higher the dose, the greater the sex

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 HALOPERIDOL

	Avoidances	Escapes	Nonresp.	Latencies	Adap-Cross	ITI-Cross
			Treatment			
Saline	0.95 ± 0.42	24.7 ± 1.27	4.35 ± 1.20	6.96 ± 0.15	9.65 ± 1.61	6.7 ± 1.32
Haloperidol 0.075 mg/kg	0.6 ± 0.27	23.1 ± 1.18	6.3 ± 1.18	7.59 ± 0.23*	7 ± 1.19	5.8 ± 1.07
Haloperidol 0.25 mg/kg	0.35 ± 1.18	13.9 ± 1.96†	15.75 ± 1.97†	8.66 ± 0.36†	6.7 ± 1.37	2.7 ± 0.8†
Haloperidol 0.75 mg/kg	0.1 ± 0.07	13.7 ± 1.85†	16.2 ± 1.85†	9.0 ± 0.28†	3.05 ± 0.7†	2.55 ± 0.5†
	NS	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.01$	$p < 0.005$
			Sex Differences			
Saline						
Males	1.5 ± 0.78	24.7 ± 1.87	3.8 ± 1.60	6.65 ± 0.24	11.3 ± 2.39	6.5 ± 1.98
Females	0.4 ± 0.26	24.7 ± 1.81	4.9 ± 1.85	7.26 ± 0.15	8.0 ± 2.16	6.9 ± 1.87
	$p < 0.05$	NS	NS	NS	NS	NS
Haloperidol 0.075 mg/kg						
Males	0.4 ± 0.40	21.9 ± 1.60	7.7 ± 1.71	7.87 ± 0.38	6.6 ± 1.75	7.6 ± 1.48
Females	0.8 ± 0.39	24.3 ± 1.72	4.9 ± 1.59	7.30 ± 0.23	7.4 ± 1.70	4.0 ± 1.40
	NS	NS	NS	NS	NS	NS
Haloperidol 0.25 mg/kg						
Males	0.4 ± 0.30	12.2 ± 2.71	17.4 ± 2.79	9.17 ± 0.61	6.5 ± 1.89	3.0 ± 1.37
Females	0.3 ± 0.21	15.6 ± 2.88	14.1 ± 2.84	8.16 ± 0.36	6.9 ± 2.09	2.4 ± 0.88
	NS	NS	NS	$p < 0.05$	NS	NS
Haloperidol 0.75 mg/kg						
Males	0 ± 0	10.1 ± 2.19	19.9 ± 2.19	9.32 ± 0.47	2.2 ± 0.84	2.1 ± 0.62
Females	0.2 ± 0.13	17.3 ± 2.61	12.5 ± 2.58	8.68 ± 0.33	3.9 ± 1.12	3.0 ± 0.98
	NS	$p < 0.05$	$p < 0.05$	NS	NS	NS

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

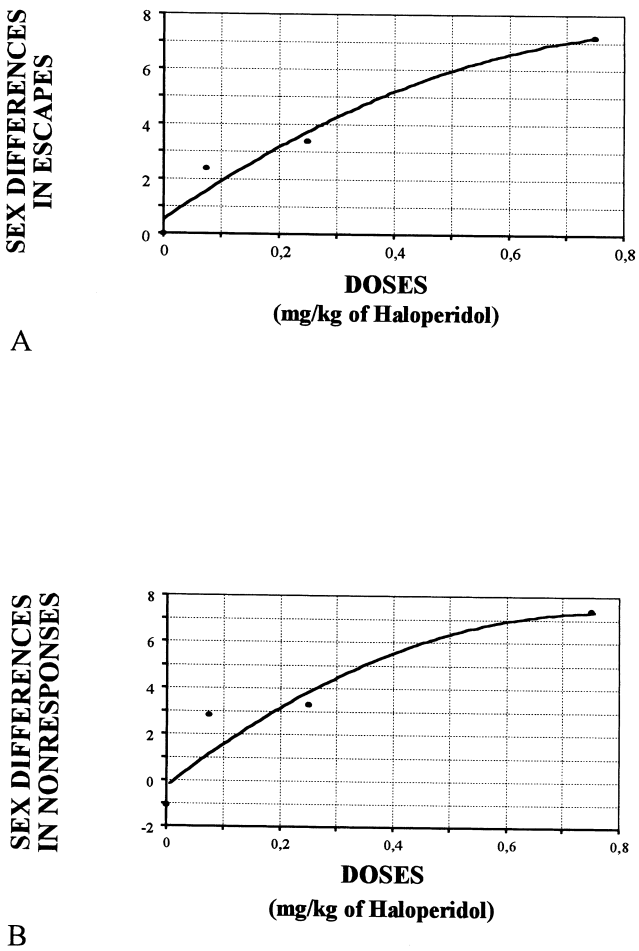

FIG. 1. Relationship between doses of haloperidol and sex differences in: (A) escapes (mean number of escapes in females minus mean number of escapes in males), the best-fit quadratic function fitted to the data is based on the equation $y = -7.9782\ X^2 + 14.86 + 0.5142$ ($r^2 = 0.938$); and (B) nonresponses (mean number of nonresponses in males minus mean number of nonresponses in females), $y = -12.492\ X^2 + 19.331\ X - 0.12585$ ($r^2 = 0.897$).

differences (see Fig. 1). This indicates that sex differences in the effects of haloperidol on escape–avoidance response in mice is a dose-dependent phenomenon.

The present results also confirm the sex differences observed in the effects of haloperidol (and other neuroleptics) in several experimental procedures with animals (4,5,8,12,17,20, 32,44,45,53) as well as with human subjects (19,28,36,43,56,57–59,61,62,68).

With respect to the origin of the sex differences observed in the action of neuroleptics, several explanations have been proposed. Three of them must be specially considered: (a) Female hormones: numerous studies suggest that central dopaminergic transmission is modulated by oestrogens (10,17, 21–23,26,27,29,34,35,37,38,40,48,51,60,63,68). Thus some measures of dopaminergic activity have been found to change across different phases of the estrous cycle. For example, in the different brain regions of the rat the turnover rates of dopamine fluctuate across the estrous cycle (38,51). Animal experiments and postmortem analyses have shown that chronic estrogen applications significantly shorten dopamine-induced behavior and reduce D_2 receptor sensitivity in the brain (27). Also, the acquisition of conditioned avoidance responses is influenced by the sexual hormone changes that occur during the rat's estrous cycle. This response improved at diestrus, but it deteriorates at estrus and metestrus (21–23).

Different hormone-related mechanisms interact with some effects of haloperidol. In this sense, the increase in the turnover of dopamine evoked by this drug has been found to be greater in the estrous phase than in other phases of the ovarian cycle (38). Other studies also indicate that behavioral responses to dopamine agonists (29,35,37) or antagonists (15,17) are affected by estrogens.

Therefore, a considerable amount of evidence seems to indicate that female hormones and central dopaminergic mechanisms interact, although how they interact remains unclear. The most important hypothesis postulates that antidopaminergic properties of estrogens have 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, e.g., after menopause (60). (b) Pharmacokinetic differences: pharmacokinetic dissimilarities between male and female schizophrenic patients, as reflected by differences in pharmacologic measures, such as homovanillic acid (HVA) and prolactin levels, have been observed. Women with chronic schizophrenia have been reported to have both higher prolactin and HVA levels while taking neuroleptics than do men, whereas higher plasma levels of neuroleptics have been found in men than in women following equivalent doses of those drugs (11, 28,61,68).

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 (25). 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 (19,59). Another possible explanation refers to different intensities of hepatic catabolism of haloperidol in males and females. Liver enzymatic activity is generally thought to be more efficient in men (59), particularly conjugation reactions, such as glucoronidation—involved in the catabolism of haloperidol—(25). This fact would not explain either the present results or previous studies (4,5, 44), where males were more affected than female by haloperidol. (c) Sensitivity to pain: it could be considered that female mice are more sensitive to pain and react more quickly to shock presentation than males (due or not to their body weight). In fact, a greater sensitivity and a lower threshold to grid shock of female rats have been described (49). If so, there should be sex differences in saline subjects; however, these differences were only found in haloperidol-treated animals in the present experiment and similar previous studies (4,5). To accept this interpretation of the facts, it would be necessary to admit that haloperidol attenuates sensitivity to shock in both sexes, and that this decrement is greater in males than in females.

Therefore, the neurochemical mechanisms involved in the origin of the sex differences in the effects of haloperidol in escape–avoidance response in mice remain unclear.

It could be argued that several sessions are necessary to properly study the sex differences in the effects of neuroleptics in escape–avoidance response, but we have previously

found these sex differences either in one (4,44) or in several sessions (5). We chose one session for the present work for economy. Also, it is important to note that the doses employed in this study are too high for repeated administration.

It has been proposed that the deleterious effects of neuroleptics on motor activity disrupt the process of initiating the response (24). The anhedonia hypothesis holds that neuroleptics interfere with conditioned responses by decreasing the reinforcing power of the stimuli (67). Also, the so-called apathy hypothesis indicates that neuroleptics produce a lack of motivation, a more general effect on learning that affects positive and negative reinforcement (1). Controversy regarding escape–avoidance response has usually been focused on whether the disruptive effects of neuroleptics are purely motor effects or if learning is also affected. As the motor explanation cannot explain why the animals trained under haloperidol but tested free of drug still show the impairment of conditioned behavior (5), we think that neuroleptics affect also the very process of learning.

No sex differences were found in the number of crossings during the adaptation period and intertrial intervals of the present experiment, both measures of the motor activity of the animals. This suggests that the sex differences observed are related to the learning process, and they are not purely due to an impairment of motor behavior.

In conclusion, the present results confirm the existence of sex differences in the effects of haloperidol in escape–avoidance response in mice as observed in earlier studies (4,5,44). These sex differences, observed in a unique training session, seem to be dose dependent and related to the learning process.

Further investigation is necessary to evaluate the generality of these sex differences. It could be considered appropriate to study larger doses of haloperidol and complete the dose–response curve for these differences. However, the substantial reduction of motor activity produced by larger doses could be an important limitation. Future studies in this field with other neuroleptics are especially necessary to check if this phenomenon is specific to haloperidol or general to antipsychotic drugs.

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