Pharmacology Biochemistry and Behavior, Vol. 44, pp. 233-236, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

BRIEF COMMUNICATION

Gender Differences in Escape-Avoidance Behavior of Mice After Haloperidol Administration

M. CARMEN ARENAS, ANDRES PARRA AND VICENTE M. SIMÓN[1]

Area de Psicobiología, Facultad de Psicología, Universitat de València, 46071 Valencia, Spain

Received 6 May 1991

ARENAS, M. C., A. PARRA AND V. M. SIMÓN. *Gender differences in escape-avoidance behavior of mice after haloperidol administration.* PHARMACOL BIOCHEM BEHAV 44(1) 233-236, 1993.—Gender differences in the disruptive effects of haloperidol on some reinforced behaviors have been observed in different species. However, the inhibitory action of haloperidol on the acquisition and performance of escape-avoidance behavior has only been investigated in male subjects. The present experiment was designed to investigate possible gender differences in the effects of haloperidol on the initial phase of an escape-avoidance learning task. Male and female mice of the OF1 strain were given a single training session in a shuttle-box. Thirty minutes prior to the behavioral test, mice were injected IP with haloperidol (0.25 mg/kg) or physiological saline (10 ml/kg). Latencies of escape and avoidance responses and the number of nonresponses, escapes, avoidances, pseudoavoidances, crossings during the adaptation period, and crossings during intertrial intervals (ITIs) were evaluated. The disruptive action of haloperidol on the escape-avoidance behavior of the mice was greater in males than in females. The number of nonresponses were higher and the number of escapes lower in treated males than in their female counterparts. These gender differences were not found in control subjects. Activity measures of spontaneous motor behavior (crossings in the adaptation period and during ITIs) did not present gender differences either. Several possible mechanisms responsible for this greater susceptibility of males to the inhibitory effects of haloperidol on escape-avoidance learning are discussed, especially the modulating role of female hormones on dopaminergic activity.

Haloperidol Gender differences Escape Avoidance Mice

IT is well established that neuroleptics produce a dose-dependent impairment in the acquisition and performance of a conditioned avoidance response. Thus, haloperidol and metoclopramide completely blocked the acquisition of the conditioned avoidance response of rats in three training sessions, while clozapine only disrupted it slightly (3). If animals received 3 days of training prior to administration of the drug, the disruptive effect was reduced but further deterioration was observed in the following days. In the same way, clozapine, haloperidol, and chlordiazepoxide decreased dose-dependent escape-avoidance response in rats trained (between 4 and 10 sessions) to avoid shock in a two-way shuttle-box. With repeated administration of these drugs, the disruptive effects of haloperidol increased, whereas those of clozapine decreased and those of chlordiazepoxide remained constant (18). Wadenberg and Ahlenius (23) compared the effects of raclopride and haloperidol on conditioned avoidance behavior in the shuttle-box. In this case, both raclopride and haloperidol produced a dose-dependent suppression of the number of avoidance responses.

These studies have in general been carried out on male subjects. Therefore, no gender differences in the effects of haloperidol on escape-avoidance behavior have been described up to date. It is known, however, that haloperidol affects some behaviors differentially in male and female subjects. For example, haloperidol decreases response and reinforcement rates more in males than in female Wistar rats trained on a differential reinforcement of low rates schedule (DRL 15 s) (22). It also increases self-administration of cocaine in female rats to a greater extent than in males (7).

In human subjects, gender differences in the effects of neuroleptics have also been described. In patients treated with

[1] Requests for reprints should be addressed to Prof. Vicente M. Simón, Area de Psicobiología, Facultad de Psicología, Avda. de Blasco Ibáñez, 21, 46010 Valencia, Spain.

phenotiazines, side effects such as akathisia and Parkinsonism appear more frequently in women than in men (with a 2 : 1 ratio) (2) whereas dystonia is more commonly found in men (20). In a 3-year survey of maintenance neuroleptic doses, Seeman (19) found that after the age of 40 women required higher doses than men, whereas younger women required lower doses than men of the equivalent age.

The present experiment was designed to investigate possible gender differences in the effects of haloperidol on shuttle-box avoidance response in mice. For this purpose, a single dose of haloperidol with known disruptive actions on escape-avoidance situations (18) was chosen and its effects were studied in both male and female mice.

METHOD

Subjects

Twenty female (23–29 g) and 20 male (31–39 g) OF1 mice from IFA CREDO (Lyon, France) were used as experimental animals. They arrived in the laboratory at 42 days of age and were housed, for 15 days, in unisexual groups of five animals in translucent plastic cages (25 × 25 × 14.5 cm) under a reversed light–dark cycle (lights off: 0930–2130 h, local time) and with controlled room temperature (22 ± 2°C).

Apparatus

A two-way shuttle-box with acrylic walls and steel bars in the floor was used (Shuttle Scan, Model SC-II, Omnitech Electronics, Inc., Columbus, OH). The box (45 × 21 × 30 cm) is bisected by a vertical partition with an opening in the middle that permits the animal to move freely from one side to the other. Infrared light beams determine the position of the animal and its crossings to the other side. The equipment was controlled by an IBM PC-XT computer using RMS V.20 of Omnitech Electronics software.

Procedure

Males and females were randomly assigned to one of four groups (n = 10): saline males, saline females, haloperidol males, and haloperidol females. Injections [0.9% saline for control subjects and 0.25 mg/kg haloperidol (Haloperidol®, Latino, Spain) for treated animals] were given IP in a volume of 10 ml/kg. Each mouse was tested once in the shuttle-box 30 min after injection (this pretreatment time was selected following the consideration that maximal brain concentrations of haloperidol are attained 15 min after injection, declining slowly afterward) (24). The test consisted of: a) 2 min of adaptation to the apparatus, in which the mouse explored the box and moved freely; b) 30 trials of two-way escape-avoidance using the following parameters: conditioned stimulus (CS)–unconditioned stimulus (US) interval, 5 s; intertrial interval (ITI), 30 ± 10 s; US intensity, 0.3 mA; maximum duration of US, 10 s. The CS (onset of light in the compartment occupied by the mouse) and US overlapped and both were response terminated. All tests were run between 1000 and 1700 h (local time). The number of crossings was measured both during the adaptation period and during the ITIs. Response latencies of trials (escapes and avoidances) were registered and subjected to analysis of variance (ANOVA) with gender and treatment as main factors. The number of nonresponses, escapes, avoidances, pseudoavoidances (15), crossings during the adaptation period, and crossings during ITIs were analyzed using the nonparametric Mann–Whitney U-test.

RESULTS

When all subjects are considered, response latencies (either escapes or avoidances) of haloperidol-treated animals were significantly longer than those of their saline controls, $F(1, 36) = 7.4$, $p < 0.01$. Likewise, the number of nonresponses ($U = 78$, $p < 0.001$) was significantly greater in the haloperidol than in the saline group. On the contrary, the number of escapes and avoidances of haloperidol-treated animals were significantly lower than those of their saline counterparts ($U = 100.5$, $p < 0.01$, for avoidances and $U = 132$, $p < 0.05$, for escapes).

Haloperidol-treated subjects made fewer crosses in the adaptation period ($U = 98.5$, $p < 0.01$) and ITIs ($U = 129.5$, $p < 0.05$) than saline controls.

In untreated animals, no statistically significant differences between genders were found in any of the parameters studied (see Table 1 for a summary of the results). However, the escape-avoidance data of treated animals showed clear sex differences. The nonparametric analysis in treated animals showed a significantly lower number of escapes ($U = 18.5$, $p < 0.025$) and a higher number of nonresponses ($U = 16$, $p < 0.01$) in males than in females. No gender differences were observed in the other nonparametric variables. Also, in the escape-avoidance latencies neither the main effect gender nor gender × treatment interaction were statistically significant ($F < 1$).

The number of nonresponses was significantly higher in treated males than in their untreated counterparts ($U = 5$, $p < 0.001$). On the contrary, the number of escapes ($U = 10$, $p < 0.001$) and adaptation crossings ($U = 24.5$, $p < 0.05$) were lower in treated than in control males. In females, haloperidol lowered the number of avoidances ($U = 20$, $p < 0.025$) and number of crossings during the adaptation period ($U = 25$, $p < 0.05$).

Other comparisons were not statistically significant.

DISCUSSION

The effects of haloperidol on different parameters of an escape-avoidance task in mice were investigated in this study, paying special attention to gender differences. Haloperidol, confirming previous findings (3,18,23), affected the escape-avoidance behavior, increasing response latencies and nonresponses and decreasing the number of escapes and avoidances with respect to control animals. Haloperidol also depressed the number of spontaneous crossings made in the adaptation time and during the ITIs. This inhibitory effect of haloperidol on spontaneous motor behavior is well documented (5,23).

The escape-avoidance data of treated animals show clear gender differences. In comparison with females, male treated subjects present significantly less escape responses and more nonresponses. Gender differences in other parameters (latencies, avoidances, pseudoavoidances, crossings during adaptation, and ITI crossing) did not reach significance (see Table 1). It seems, therefore, that, at least in this experimental situation, the inhibitory effects of haloperidol on this behavior are stronger on males than on females. (It must be noted that the lower number of escapes of males is not due to a relative increase of avoidances but to a greater number of nonresponses.)

Gender differences were found only in animals that combine two circumstances: having been treated with haloperidol and being in the avoidance situation. For example, no significant gender differences ($U = 30$, n.s.) were found in the number of crossings of haloperidol-treated animals, although dif-

TABLE 1

MEAN LATENCIES OF ESCAPE AND AVOIDANCE RESPONSES (LAT) WITH SD AND SIGNIFICANCE LEVELS OF ANOVA: TOTAL NUMBER OF ESCAPES, AVOIDANCES, PSEUDOAVOIDANCES (PSEUDOAVO), NONRESPONSES (NONRESP), CROSSINGS DURING THE ADAPTATION PERIOD (ADAPT-CROSS), AND CROSSINGS DURING ITIs (ITICROSS) WITH SIGNIFICANCE LEVELS OF THE MANN-WHITNEY *U*-TEST

	Escape-Avoidance Responses						
	LAT ± SD	Escapes	Avoidances	Pseudoavo	Nonresp	Adapt-Cross	ITI-Cross
Effects of treatment							
Saline							
All animals	7.0 ± 1.1	537	17	10	36	187	212
Haloperidol							
All animals	7.8 ± 0.8	388	4	4	204	115	78
Significance	$p < 0.01$	$p < 0.01$	$p < 0.05$	n.s.	$p < 0.001$	$p < 0.01$	$p < 0.05$
Gender differences							
Saline							
Males	7.2 ± 0.9	272	5	6	17	77	101
Females	6.8 ± 1.2	265	12	4	19	110	111
Significance	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Haloperidol							
Males	7.8 ± 1.1	139	4	0	157	50	44
Females	7.8 ± 0.5	249	0	4	47	65	34
Significance	n.s.	$p < 0.025$	n.s.	n.s.	$p < 0.01$	n.s.	n.s.
Effects of treatment in each gender							
Saline vs. Haloperidol*							
Males		$p < 0.001$	n.s.	n.s.	$p < 0.001$	$p < 0.05$	n.s.
Females		n.s.	$p < 0.025$	n.s.	n.s.	$p < 0.05$	n.s.

*For relevant data see above.

ferences in ambulation of intact males and females when introduced in a novel environment are documented (1,11). Likewise, neither the escapes and nonresponses of male and female controls nor the spontaneous crossings of male and female haloperidol-treated animals were significantly different. In fact, males appeared more inhibited by haloperidol than females only in the induced behavior, but not in the spontaneous behavior (adaptation and ITIs crossings).

In control animals, no differences in escape-avoidance responses between males and females were found, although such differences have been described elsewhere (1,21). It is possible that gender differences in untreated animals only become evident after several training sessions, as has been observed in other experiments at our laboratory.

The possibility that differences in body weight might partially account for the observed gender differences is unlikely. The correlation between body weights and nonresponses of the 20 haloperidol-treated subjects is quite high ($r = 0.53$, $p < 0.02$). This could be an indication that body weight is involved. However, if body weight by itself could explain the mentioned sex differences one would expect to also find an equally high correlation in untreated subjects. This is not the case. The correlation between body weights and nonresponses of the 20 saline controls is low ($r = 0.1$, n.s.).

The results concerning escape-avoidance responses agree with those reported by van Hest et al. (22). Rats, running under a DRL schedule in an operant chamber, showed dose-dependent decreases in response and reinforcement rates after haloperidol administration. Males were more sensitive to the inhibitory effects of the drug than females. In contrast, Dalton et al. (7) reported that female rats were more sensitive to haloperidol than males in terms of increases in cocaine self-administration. In the present and van Hest (22) studies, the haloperidol effects are behaviorally inhibitory, whereas the Dalton study (7) involves apparently behavioral excitation.

A number of possible explanations must be considered to account for the gender differences described above. One possibility could be that female mice are more sensitive to pain and react more quickly to the shock presentation than males. A greater sensitivity and a lower threshold to grid shock of female rats have, in fact, been described by Paré (16). However, this interpretation does not elucidate why this difference is only found in haloperidol-treated animals and is not also present in saline controls. To accept this interpretation of the facts, it would be necessary to admit that haloperidol attenuates sensitivity to shock in both sexes (thus decreasing the number of responses, compatible with the results) and that this decrement is greater in males than in females. Although no clear analgesic action of haloperidol as such has been described, neuroleptic drugs are well known to produce a certain "disinterest" or "indifference" toward environmental stimuli (14).

Another possible explanation would refer to different intensities of hepatic catabolism of haloperidol in males and females, as has already been shown for imipramine and diazepam (8). In fact, it has been reported that following equivalent doses of neuroleptics blood levels were higher in men than in women (4).

A number of experimental results suggests that central dopaminergic function may be modulated by female hormones. This mechanism must be considered as a possible explanation for the gender differences observed in the effects of haloperidol on escape-avoidance behavior. Thus, some measures of dopaminergic activity have been found to change across different phases of the estrous cycle. For example, in different

brain regions of the rat turnover rates of dopamine (DA) fluctuate across the estrous cycle (13,17).

In experiments in which estrogens are administered, they seem to influence different dopaminergic mechanisms. The number of DA receptor sites (labeled by [^{3}H]spiroperidol) increases in estrogen-treated male rats previously injected unilaterally with 6-dihydroxydopamine (6-OHDA) into the substantia nigra (10).

Other studies also indicate that behavioral responses to dopamine agonists (9,10,12) or antagonists (6,7) are affected by estrogens. Thus, Harrer and Schmidt (9) observed that in male ferrets prior estradiol treatment potentiated some behavioral effects of apomorphine, such as the inhibition of predatory behavior and the apomorphine-induced stereotypies. And, in the rat rotation model duration of amphetamine-induced rotation increased significantly 5–8 days after treatment with 17β-estradiol (10).

Different hormone-related mechanisms interact with some effects of haloperidol. In this sense, the increase in turnover of DA evoked by this drug has been found to be greater in the estrous than in other phases of the ovarian cycle (13). Likewise, Dalton et al. (7) observed that a single injection of the antiestrogen tamoxifen caused an attenuation of the increasing effect of haloperidol (0.1 mg/kg) on cocaine self-administration of female rats. Therefore, a considerable amount of evidence seems to indicate that female hormones and central dopaminergic mechanisms interact, although the direction of this influence remains unclear.

It can be concluded that the effects of haloperidol on an escape-avoidance task present interesting gender differences that do not appear to be purely due to an impairment of motor behavior. Nevertheless, the temporal course of such differences across several training sessions and the neurochemical mechanisms involved require further investigation.

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