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Sex Differences in the Effects of Neuroleptics on Escape-Avoidance Behavior in Mice: A Review

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PARRA, A., M. C. ARENAS, S. MONLEÓN, C. VINADER-CAEROLS AND V. M. SIMÓN. *Sex differences in the effects of neuroleptics on escape-avoidance behavior in mice: A review.* PHARMACOL BIOCHEM BEHAV **64**(4) 813–820, 1999.—The literature of the effects of dopamine antagonists on escape-avoidance, focusing on data obtained in our laboratory with male and female mice, is reviewed. The acute administration of haloperidol, raclopride, clozapine, and SCH 23390 impaired escape-avoidance behavior more in males than in females, and the subchronic administration of haloperidol had a similar effect. This appeared to be a reliable phenomenon, because it was observed in both kinds of administration, in two mouse strains, and with several drugs and doses. The observed results were dose dependent, although the dose–effect relationship was not the same in all drugs. The sex differences in escape avoidance did not seem related to sex differences in the well-known deteriorating effects of these drugs on motor activity. In addition, an analysis of all our studies showed that there were no sex differences in the variability of responses, reinforcing the idea that female subjects should be included in these types of studies. © 1999 Elsevier Science Inc.

Escape Avoidance Haloperidol Raclopride Clozapine SCH 23390 Sex differences

THE existence of sex differences in reproductive and nonreproductive behaviors indicates that males and females have adopted some different strategies in their adaptation to the environment throughout evolution (24). The ontogenetic approach holds that sex differences in behavior are due to organizing and activating effects of sex hormones on the nervous system, although some differences cannot be explained without the concourse of such effects on bone and muscular systems. Sexual dimorphism can be observed in many levels and cases, for instance, in anatomy: genitalia (57) and size of certain brain areas (77); in physiology: presence of reproductive cycles of females (49), and hepatic metabolism (59); and behavior: sexual (9), and nonsexual (10).

In psychopharmacology, individual differences like age or cardiovascular functioning are regularly taken into account; however, sex should also be included as one of these variables, because it is important to know if a given drug has the same effects on males and females. Nevertheless, most of the preclinical trials involve only males, on the basis of a supposed higher variability of the females, although women consume more psychotropics than men (18). In fact, phases 1 and 2 of clinical trials are carried out mainly in men. In the United States there were guidelines dating from 1977 (48) asking for the use of only males in clinical trials. Lately, new guidelines dating from 1993 (47) suggest the use of women and minorities in phase 3. The reason for the use or not of males and females should not be based on politics, but on scientific rationale. The use of both male and female subjects is specially relevant in animal studies of disorders in which sex differences have been described in human beings. In fact, there are sex differences in schizophrenia (which is the most important clinical use of neuroleptics) at several levels: the prevalence is higher (43) and the age of onset is earlier (2) in men than in women; women show a larger cerebral hypoplasia than men (63); and women may be less vulnerable to particular cognitive deficits (35), although this last difference could be attributed to the severity of symptoms, not to sex differences in neuropsychological functioning (38). Furthermore, sex differences in the effects of neuroleptics on schizophrenia have also been described: women under age 40 respond better to and require lower doses of these drugs than men; this advantage tends to disappear with increasing age (65,78). Also, some sex

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differences in the side effects of neuroleptics have been reported: acute dystonias are more frequent in men than in women (at a 2:1 ratio), as informed by Ayd in a classic survey (7) and confirmed by Swett (72), while parkinsonism and akathisia are more frequent in women than in men (7).

Nevertheless, a decade ago, when the work reviewed here was started, the preclinical studies on the effects of neuroleptics on escape-avoidance behavior were run only on male subjects [e.g., (13,37,62)]. By that time, in our laboratory, we were involved in the research effort to improve the knowledge of the behavioral profile of certain substances, most of them having a long history of clinical use, such as the neuroleptics haloperidol, chlorpromazine, or sulpiride. We were studying aggression in a clearly ethopharmacological frame (69). Then we broadened the scope of the laboratory to include a technique, escape-avoidance response in a shuttlebox, coming from the experimental psychology tradition (36). This behavioral paradigm has a long and strong bonding to the study of the effects of neuroleptics on animal behavior (23,44), to our knowledge, using only male subjects. In these new studies, we decided to include females because the involvement of both kinds of subjects is more representative of nature. In this field, nature says that there are sex differences in the epidemiology of several psychiatric disorders including schizophrenia and the effects of neuroleptics in human beings [see above and (66,74)]. We chose mice as experimental subjects because (a) we were using these animals in aggression experiments, (b) they were cheaper than rats, and (c) there were less data in the literature obtained with mice than with rats.

In the present article we review the literature of the effects of neuroleptics on (a) learning procedures other than escape avoidance in males, (b) escape-avoidance behavior in males, (c) behavioral tasks other than escape avoidance in males and females, and (d) escape-avoidance behavior in male and female mice. Part (d) deals with works entirely performed at our laboratory.

LEARNING PROCEDURES OTHER THAN ESCAPE-AVOIDANCE IN MALES

There is a strong body of evidence that neuroleptics interfere with a wide variety of learning procedures: one-way active avoidance (33), two-way avoidance (1), lever-press avoidance (44), Sidman avoidance (55,56), escape behavior in a runaway (19), inhibitory avoidance (21), spatial learning (58), classical eye-blink conditioning (64), operant lever pressing for water (45), operant running for food (40), intracranial self-stimulation (53), and place preference for food (71). How ever, in a few instances, neuroleptics appear to act in the opposite way, i.e., favoring learning: self-administration of cocaine (25), and latent inhibition (61). Also, bidirectional effects of neuroleptics on lever pressing for food depending on the dose administered have been reported (70).

ESCAPE-AVOIDANCE BEHAVIOR IN MALES

In most of the studies dealing with the effects of drugs on behavior, male subjects are used because the activity levels of these animals are not subjected to the cyclic oscillations of their female conspecifics. As the specificity of the effects of neuroleptics on avoidance vs. escape behavior inhibition of avoidances at doses that have no effect on escapes, is well established (16,62), it has been claimed as an animal model of the antipsychotic effects of these drugs (20). Nevertheless, some data reveal that the selective inhibitory effects on avoidance behavior is also present in nonneuroleptic CNS depressant drugs such as chlordiazepoxide or pentobarbital (60). Even in the case that the specificity of the inhibitory effects of neuroleptics on escape-avoidance behavior were not a good animal model for the study of the antipsychotic properties of these drugs, this effect deserves the attention of researchers because it could be an interesting procedure to study the effects of these drugs on learning and memory. The escape-avoidance paradigm could be a model of a possible side effect—impaired learning and memory—instead of, or in addition to, a model of antipsychotic action.

SEX DIFFERENCES IN PARADIGMS OTHER THAN ESCAPE-AVOIDANCE

Sex differences in the effects of neuroleptics in several paradigms other than escape avoidance have been found. For instance, haloperidol produces different effects on body weight and temperature, depending on the sex of the animals: males tend to lose weight while females tend to gain it; and a reduction of body temperature is observed only in female rats (8,26). In catalepsy produced by haloperidol, a common animal model for the extrapyramidal effects of neuroleptics, females are more affected by the drug than males [e.g., (54)]. In conditioned responses the observed sex differences seem to be dependent on the action of the drug: females are more sensitive than males when it has activating effects, like cocaine self-administration (25); but males are more sensitive when inhibition of responses is required, like in a differential reinforcement of low rates schedule (DRL 15 s) (75).

SEX DIFFERENCES IN ESCAPE-AVOIDANCE IN MICE

As far as we know, apart from those of our laboratory, none of the studies dealing with the effects of neuroleptics on escape-avoidance behavior have included and compared such effects in male and female subjects. This kind of studies are interesting because of the above-mentioned sex differences in schizophrenia, and because the specificity of neuroleptics to inhibit avoidances at doses that do not modify escapes is perhaps the oldest behavioral assay to test these drugs (23).

The general procedure of our experiments included the use of male and female mice, housed separately by sex in boxes of four to five subjects, with food and water ad lib in standard laboratory conditions. In a typical session, the subjects were submitted to 30 trials of escape avoidance in a two-way shuttlebox, with intertrial intervals (ITIs) of 30 $\pm$ 10 s. Each trial consisted of the presentation of a light (6 W) located in the ceiling of the compartment occupied by the mouse, which, after 5 s, overlapped a 0.3-mA foot shock of 10 s duration. An escape response was defined as crossing to the opposite side during the shock period, and an avoidance as crossing during only the light period. Escape and avoidance responses terminated the trial. If the mouse did not cross to the other side, receiving the full 10-s shock, a nonresponse was computed. The behavioral parameters taken into account were: number of escapes; number of avoidances; number of nonresponses; latencies of escapes; latencies of avoidances; number of crossings during the adaptation period; and number of crossings during the ITIs. The first five measures are closely related to stimuli, and are considered specific, and the remaining two are examples of spontaneous motor activity and are considered nonspecific to the situation. Number of escapes, number of avoidances, number of nonresponses, and crossings during the ITIs will be considered in this review. Drugs were IP administered in a volume of 0.01 ml/g body

weight, and the animals injected 30 min before the shuttlebox session.

Acute Administration of Haloperidol, Raclopride, Clozapine, and SCH 23390

The results obtained in our experiments using dopamine antagonists on male animals are in keeping with those generally described in the literature. In the present work we are going to discuss the sex differences observed with each one of the studied drugs.

Different doses of acutely administered haloperidol were used in OF1 mice: 0.075 mg/kg (51), 0.25 mg/kg (3,50,51), and 0.75 mg/kg (51). The scarcity of avoidances in a unique session limits the value of this important parameter. The first study that we carried out (3) showed the strongest sex differences. The disruptive effect of haloperidol was clearly observed in all animals irrespective of sex, although it was greater in males than in females. Specifically, the number of nonresponses was higher, and the number of escapes lower, in treated males than in their female counterparts. These sex differences were not found in control animals. ITI crossings, a spontaneous motor activity measure, did not show sex differences in any of the comparisons. The absence of sex differences in escapes and nonresponses in controls, and in spontaneous motor activity in treated animals, leads us to think that the sex differences observed in treated animals are related to the action of haloperidol on escape but not to its impairment of general motor activity.

When we explored the generality of the sex differences observed by Arenas et al. (3) in a different strain of mice, the BALB/c (50), sex differences were found in the number of escapes and nonresponses in controls: males had more escapes and less nonresponses than females. The disruptive effect of haloperidol, producing less escapes and more nonresponses, was observed only in males and not in females. In fact, haloperidol neutralized the sex differences observed in salines. In ITI crossings, no statistically significant sex differences were found at all.

In a further study in OF1 mice (51), in which several doses of haloperidol were administered (0.075, 0.25, and 0.75 mg/kg), a dose-dependent effect was observed in escapes, nonresponses, and ITI crossings in all animals. The impairing effect of haloperidol was statistically different in males and females at the highest dose in escapes and nonresponses. Nevertheless, its effects on ITI crossings did not show sex differences at any of the doses. Males made less escapes and more nonresponses than females. At the lower doses the effect did not reach the level of statistical significance.

In that study, we introduced a new analysis of the sex differences in the effect of haloperidol. The one utilized until then included parametric and nonparametric statistics. In both cases the result is dichotomic: yes or no; "yes" for statistically significant differences ($p < 0.05$), and "no" for statistically nonsignificant differences ($p > 0.05$). The relationship between doses of haloperidol and sex differences can be studied with a mathematical analysis that gives "smooth" results. We obtained the equation on which the best-fit quadratic function fitted to data is based. The analysis was performed for escapes, where data were the mean number in females minus the mean number in males, and nonresponses, where data were the mean number in males minus the mean number in females. In both parameters a high positive correlation between the doses of haloperidol and the observed sex differences was obtained, and we concluded that the higher the dose, the greater the sex difference [see Fig. 1 in (51)].

A later study (52) was designed to check the generality of the sex differences found in previous studies with other dopamine antagonists. The drugs were selected according to their affinity for D_1 and D_2 dopamine receptors: raclopride, a highly selective D_2 antagonist (32); clozapine, a nonselective antagonist with comparable D_1-D_2 affinities (17); and SCH 23390, a specific D_1 antagonist (41). The first two drugs are used as antipsychotics, and the last one does not have such an effect.

The results of raclopride (0.4, 1.2, and 3.6 mg/kg) were very similar to those described above for haloperidol: a clear dose-dependent effect of the drug in every behavioral measure, sex differences in escapes and nonresponses at the highest dose, and a very high positive correlation between the drug doses and the observed sex differences. Perhaps a minor difference between the effects of raclopride and haloperidol is that the two lower doses of raclopride do not seem to produce any difference at all as compared with salines [see Fig. 1, both in (51) and (52)]. In ITI crossings, no statistically significant sex differences were found at all.

The clozapine (1, 3, and 9 mg/kg) results, as expected, showed some differences from that of haloperidol and raclopride. There was no statistically significant effect on ITI crossings, a measure of spontaneous motor activity. Clozapine has shown less motor effects than typical neuroleptics in other tests (34,39,42). The direction of sex differences observed with this drug was the same as with haloperidol and raclopride, with the males being more sensitive to the disruptive effect of the drug. Nevertheless, sex differences were also present at the intermediate dose, statistically significant in escapes, and almost significant in nonresponses. The correlation between the drug doses and the observed sex differences was not so high as in haloperidol and raclopride, and the intermediate dose seems as effective as the highest one in producing sex differences [see Fig. 2 in (52)].

In the case of SCH 23390 (0.06, 0.2, and 0.6 mg/kg), the same deteriorating effects as in previously discussed drugs were found in all subjects, including ITI crossings in this case. The particularity of SCH 23390 is that the low and high doses, but not the intermediate one, produced significant sex differences in escapes and nonresponses. This is the reason for low correlations between doses of drug and sex differences observed. No statistically significant sex differences were found at all in crossings during ITIs.

Subchronic Administration of Haloperidol

More than one training session is needed to assure that learning has taken place, i.e., the number of avoidances increases. This is the reason why we tested mice daily for 5 days. The subjects behaved under the effect of 0.075, 0.1, and 0.2 mg/kg of haloperidol, given IP 30 min before the behavioral test. There were separate control groups for the 0.075 mg/kg, and the other two doses, due to the fact that experiments were run at different times and were reported as two separate studies (4,6).

The 0.075 mg/kg of haloperidol clearly impaired avoidance learning in males but did not attain the same degree of impairment in females [see Table 1 in (4)]. Also, males made less escapes and more nonresponses than females. To interpret the observed sex differences, one has to take into account that saline males made more avoidances and more ITIs than their counterpart females (see and compare Fig. 1a and b). The higher number of avoidances in control males than in females

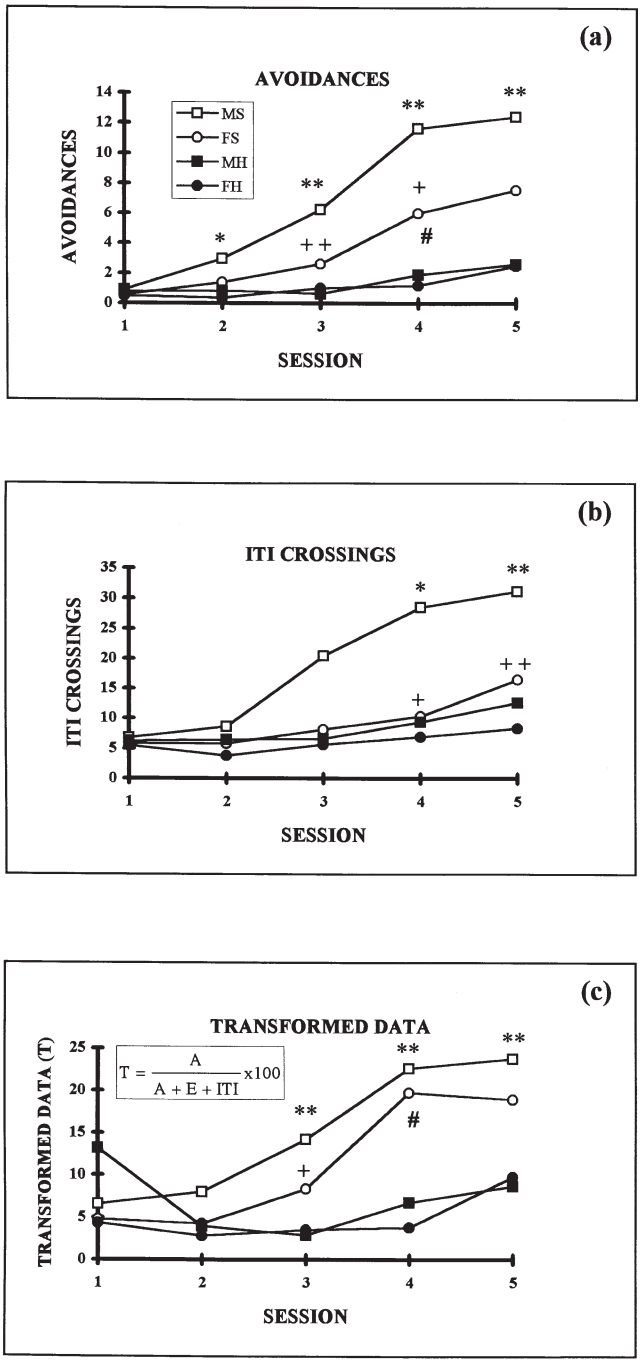

FIG. 1. (a) Mean number of avoidances. (b) Mean number of crossings during the intertrial intervals, ITI. (c) Mean percentage of avoidances over the total number of crossings: avoidances, A; escapes, E; and crossings during the intertrial intervals, ITI. Based on data of five sessions of escape-avoidance conditioning in a two-way shuttle-box. MS, male salines; FS, female salines; MH, male haloperidol; FH, female haloperidol; *$p < 0.05$, **$p < 0.01$ compared with MH; +$p < 0.05$, ++$p < 0.01$ compared with MS; #$p < 0.05$ compared with FH (Mann–Whitney *U*-tests).

makes the inhibitory effects of haloperidol easier to appear in males than in females, i.e., there is more room for the impairing action of haloperidol.

In the 1-day studies (see above) there was a clear lack of relationship between escape behavior and ITI crossings (the last one taken as a measure of general motor behavior). However, in the 5-day studies the lack of relationship between avoidance, the relevant measure here, and ITI crossings is not clear. The similarities between the shapes of avoidance and ITI curves can be seen when comparing Fig. 1a and b. Remember that ITIs are not a measure of learning. The relationship between avoidances and ITIs can be further studied applying a formula to transform the Arenas et al. data (4). The formula, suggested by one of us (A.P.), allows us to see the results in terms of percentage of responses that are avoidances over the total number of crossings. It was applied for the first time to analyze the apparently contradictory effect of scopolamine, a learning and memory impairing substance that clearly increases the number of avoidances (76):

$$T = \frac{A}{A + E + ITI} \times 100$$

where T = transformed data (per animal per day), A = number of avoidances, E = number of escapes, and ITI = number of ITIs.

It is interesting to note that, when considering the transformed data, less marked differences are found than when using direct data, although it is still possible to state that control males avoid shocks better than females, and that haloperidol has more impairing effects in males than in females (see Fig. 1c).

We think that measuring crossings during the adaptation period and the ITIs at the same time as we are measuring escapes, avoidances, and nonresponses, is useful to properly attribute the causes of changes observed in the induced behaviors. If differences between two groups are found in avoidances or nonresponses, a control for spontaneous motor activity is needed. Both above-mentioned measures are a good control for such a purpose, but it is interesting to note that both, specially the ITIs, evolve throughout the sessions. In fact, their curves have the learning curve shape [see performance of saline groups in the figures and tables of (4,6,76)]. The reason for this could be found in a progressively diminished anxiety due to the familiarity with the situation. The learning curve shape of the number of avoidances is not a guarantee that learning has taken place. Transforming direct data (considering the changes in percentage of crossings that are avoidances over the total number of crossings, see above) to make a measure of learning, is appropriate when there are differences (sex differences in our case) in the spontaneous motor measures. When there are no such differences the sexual dimorphism in avoidances can be considered a specific drug effect.

Another study (6) was carried out with the aim of exploring if moderately higher doses of haloperidol (0.1 and 0.2 mg/kg/day) were capable of producing clear impairing effects in females and if, at these doses, the sex differences were still evident. We followed a similar procedure to that employed in Arenas et al. (4). The results did not show sex differences in the deteriorating effects of this dopamine antagonist in any of the behaviors studied, but a tendency in the number of nonresponses was observed in the same direction as in former results: male animals were more sensitive than females to the inhibitory effect of the 0.1 mg/kg dose of haloperidol. This tendency can also be observed in the number of days in which haloperidol-treated animals made significantly less ITI cross-

ings than their saline controls: males, 4 (0.1 mg/kg) and 5 (0.2 mg/kg) days; and females, 2 (0.1 mg/kg) and 3 (0.2 mg/kg) days [see Table 1 in (6)]. In this experiment the formula was applied to data and gave the same results (not shown) as the direct data reported in Arenas et al. (6); note that sex differences in the number of avoidances and ITI crossings in control groups were not observed in that study.

In general, the doses of 0.1 and 0.2 mg/kg tend to abolish the differences found with 0.075 mg/kg, although in the mean number of avoidances the 0.1 mg/kg dose represents the inflexion point for the inverted "U" in the magnitude of sex differences in avoidance [see Fig. 2 in (6)].

DISCUSSION

The above-reviewed literature leads us to two main observations: 1) the impairing effects of neuroleptics on escape-avoidance in mice are sexually dimorphic. They are observed in males and females, but are more pronounced in the former. 2) The sex differences found in the effects of dopamine antagonists in escape-avoidance behavior are not purely due to a differential impairment of motor behavior.

A summary of the observed sex differences in the effects of acutely administered neuroleptics on escape-avoidance is: (a) haloperidol (0.075, 0.25, and 0.75) mg/kg impaired escape-avoidance behavior, showing less escapes and more nonresponses in treated animals compared with controls. This effect is stronger in males than in females. The differences in the strength can be observed sometimes in comparisons between groups of haloperidol-treated males and females, or by the presence of the impairing effect in males and not in females. These sex differences should not be attributed to nonspecific effects on spontaneous motor activity because there were no sex differences in the impairing action on ITI crossings. With respect to the doses, the effect of 0.075 mg/kg did not reach statistical significance, but in general, the higher the dose the greater the sex differences in escapes and nonresponses. (b) Raclopride (0.4, 1.2, and 3.6 mg/kg) produced similar results to haloperidol, but statistically significant sex differences were found only at the high dose. (c) Clozapine (1, 3, and 9 mg/kg) showed similar effects to that of haloperidol and raclopride, although the intermediate dose proved to be almost as effective as the high one. (d) SCH 23390 (0.06, 0.2, and 0.6 mg/kg) had sexually dimorphic effects at the low and high dose, but not at the intermediate one. The direction of the differences was the same as with the other substance.

With respect to sex differences in the effects of subchronic administration of neuroleptics on escape avoidance, tested with haloperidol (0.075, 0.1, 0.2 mg/kg), the main results are those obtained in avoidances. Clear sex differences in the effect of haloperidol were found at the low dose: males were more affected than females. Little effect was observed at the intermediate dose, and no sex differences were present at the high dose. In this procedure of administration it can be said that the lower the dose, the greater the sex differences. It seems opposite to the effect pointed out for acute administration. Nevertheless, one must take into account the relevant measures in both cases are not the same (escapes vs. avoidances), and that the high doses of haloperidol given repeatedly produced a strong motor behavior impairment in males and females, perhaps leading to a floor effect with no room for appreciating sex differences in the learned behavior (i.e., small number of avoidances).

The possible explanations for the sex differences summarized here must be searched for in paradigms very different from our own. Numerous studies have suggested that central dopaminergic transmission is modulated by estrogens (15). In a recent study, Díaz-Véliz et al. (29) report the effects of dopamine agonists and antagonists on conditioned avoidance response (CAR) in various hormonal status: diestrous, estrous, ovariectomized, and ovariectomized plus estrogen replacement. Several interesting observations can be obtained from this work. The hormonal status by itself affects the level of CAR, as can be seen in groups that did not receive agonist or antagonist dopamine receptor treatment. Drug effects have different directions, improving or impairing CAR, depending upon the hormonal status. These findings are difficult to interpret because a dopamine agonist (PPHT) and a dopamine antagonist (SCH 23390) can produce a similar effect on CAR (29).

The precise mechanism of the modulatory action of estrogens on dopamine is still unknown. The observed sex differences in various aspects of schizophrenia (see above) have been interpreted as a consequence of antidopaminergic properties of estrogens playing a protective role in this disorder (67). In our experiments, females are less impaired by neuroleptics than males. It could be the case that estrogens, modulating the dopamine receptor functioning, attenuate the action of any acting substance, dopamine, or drug, on such receptors. In one experiment we hypothesized this protective role of estrogens and tested the effects of haloperidol 0.075 mg/kg on escape-avoidance in ovariectomized and sham-operated females. As the dose utilized had little impairing effect, there was no room for the unprotective role of ovariectomy in controls, but in a few parameters the ovariectomized animals showed greater impairing effects of haloperidol than controls (5). However, further studies (e.g., dealing with antiestrogen-treated females) are needed to verify the hypothesis of the involvement of female sexual hormones.

Although the effects of estrogens on dopamine neurotransmission have attracted much of the attention when studying the sex differences of neuroleptics, other neurotransmitters have to be taken into account. Neuroleptics, besides their main action on dopamine receptors, also interfere with serotonin neurotransmission (73). On the other hand, there is some evidence that estrogens and progesterone modulate serotonin neurotransmission (46). Therefore, it is possible that the responsibility for the sex differences in the effects of neuroleptics must be shared by more than one neurotranmission system.

In our experiments, females were not checked for their stage of the estrous cycle, although it has been argued that checking this phase is needed in studies that involve females. However, we think that it has to be done when the hormonal status is an independent variable as is the case, for instance, in Díaz-Véliz et al. (29), but when it is an intermediate variable, randomly distributing subjects to groups and establishing the order in which the animals are tested counterbalance the possible influence of different hormonal status.

In the search for an explanatory hypothesis for sex differences in the impairing effects of neuroleptics on escape-avoidance behavior, a peripheral origin for the differences cannot be ruled out. There are sex differences in drug metabolizing enzyme activities, being 40–100% higher in female than in male mice. These sex differences result from differential expression of several hepatic forms of cytochrome P450. These enzymes are sex-dependent but are not directly regulated by sex hormones. The sex-dependent growth hormone regulates their activity (68). As a result of sex differences in the first-pass metabolism, less neuroleptic would be available to central dopamine receptors, and the behavioral effects would be

less in females than in males. The central or peripheral places for the origin of sex differences in the effects of neuroleptics on behavior is an important issue that deserves further attention.

There is a general belief that data obtained in females show higher variability than those obtained in males. Perhaps this belief is based on the fact that females show different results in several behavioral tests, depending on their stage of the estrous cycle (10,14,27–29). Most of the studies use only males to avoid the complexities of female biology. It is reasonable that these hormonal variations throughout the reproductive cycle produce higher variance in behaviors modulated by such hormones. The inclusion of female subjects in experiments tends to be avoided because their general activity (which shows cyclic variations) (10) can modify many other behaviors. Nevertheless, many observations from our laboratory are in contradiction with such a belief. Looking at tables published in (3,4,6,50–52) there appear 171 pairs of standard error of means (SEM); one member of each pair is from a male group, and the other from its female counterpart. In 97 cases the SEM was higher in males than in females, in 73 cases the opposite was true, and in one case both members of the pair were equal. Furthermore, if the variability of females were dependent on hormonal variations of the reproductive cycle, the ovariectomized subjects of Arenas et al. (5) would have shown lower SEMs than their sham-operated counterparts. The data do not confirm the hypothesis: the SEM of controls were higher than that of ovariectomized animals in 16 out of 30 cases.

The second main observation referred to at the beginning of the present section is that the sex differences found in the effects of dopamine antagonists on escape-avoidance behavior are not purely due to a differential impairment of motor behavior. This is related to the old problem of dissociating learning and performance in the explanation of the effects of drugs on learning (12,22), due to their reducing or enhancing effects on locomotor activity (11,31). This kind of dissociation is more complicated in studies involving male and female subjects because of the (sometimes) observed sex differences in spontaneous motor activity or even in avoidance learning in nontreated animals (10,30). Nevertheless, in relation to our results, we believe that the sex differences are based on the effects of drugs on specific measures. The impairing effects of the tested drugs on motor activity (crossings during adaptation period and ITIs) were similar in males and females, while in the case of specific measures (escapes, avoidances, and nonresponses) the effects were more pronounced in males. In fact, there were few sex differences in both kinds of measures in saline animals, whereas in treated ones differences appeared in specific but not in motor activity measures.

CONCLUSIONS

The existence of sex differences in the effects of neuroleptics on escape-avoidance behavior in mice, where males appear more impaired than females, is: 1) a reliable phenomenon because it is observed in: a) acute and subchronic administration, b) OF 1 and Balb/c mouse strains, c) several doses, and d) different drugs that have different affinity for specific dopamine receptor subtypes. 2) Dose dependent, although the dose–effect relationship is not the same across drugs. 3) Independent of sex differences in the impairing effects on spontaneous motor activity.

The reasons for such differences are yet unknown, but constitute an experimental observation that gives support to the importance of including female subjects in the preclinical pharmacological studies.

Even though there is a general belief that female subjects show more variability than males, an analysis of all our studies did not detect any sex difference in the variability of responses, reinforcing the idea that female subjects should be included in these types of studies.

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