Original Paper

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The Effect of Intrauterine Antipsychotic Drug Exposure on Learning and Memory in Adult Rats

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ABSTRACT:

The effect of intrauterine antipsychotic drug exposure on learning and memory in adult rats

Objective: The effects of antipsychotic drugs, of whose different classes can be used in the treatment of patients with resistant to schizophrenia, on the fetus and the benefits of the treatment to the mother should be taken into consideration before making a decision about initiating treatment. This study aimed to examine the effects of prenatal exposure to various antipsychotic agents on learning and memory in adult rats.

Method: In this study, antipsychotic drugs from different chemical classes (2 mg/kg haloperidol, 100 mg/kg thioridazine, 200 mg/kg sulpiride, 20 mg/kg chlorprothixene, 40 mg/kg clozapine, 10 mg/kg fluphenazine, 20 mg/kg chlorpromazine) and water for the control group were administered to pregnant Sprague-Dawley dams through gavage during the pregnancy period. In total, 16 groups were created and tested in the Morris water maze by dividing offspring of eight mother rats into male and female rat groups (n=10) on postpartum day 60. Learning was tested with hidden platform task and memory was tested with probe test.

Results: It has been observed that learning was impaired in the male and female groups that received haloperidol, sulpiride, chlorprothixene, clozapine, and chlorpromazine, as well as in the female groups receiving fluphenazine and thioridazine. Thigmotaxis is the time spent on 10 cm perimeter of the walls of the pool. Thigmotaxis values of all groups were still higher except for the male group of thioridazine on fifth day.

Conclusion: These results show that when prenatal exposure to antipsychotics occurs, it causes impairment in the realization of task of finding escape platform properly, rather than affecting learning and memory functions, specifically in their adulthood so that high thigmotaxis may be the reason for deterioration in escape latency parameter.

Keywords: learning, memory, antipsychotics, haloperidol, sulpiride, thioridazine, chlorprothixene, chlorpromazine, clozapine, fluphenazine

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INTRODUCTION

Antipsychotic drugs are used for treatment of psychosis like schizophrenia that occurs mostly in the mid to late 20s which is peak of childbearing years[1]. Different classes of antipsychotics should be administered to patients with schizophrenia in case of resistance to treatment. Some female patients take these medications while being aware of that they are pregnant; however, the others take them without being aware of their pregnancy.

Maintaining antipsychotic medication during pregnancy still remains as a dilemma because the effects of antipsychotics on the fetus and the results of untreated psychosis must be considered and weighted carefully. Moreover, the risks and

benefits of agents on pregnant patients with schizophrenia should be evaluated before making a decision about starting a treatment[2]. Both starting antipsychotic treatment and leaving the psychosis not be treated have some risks. Without treatment psychosis can cause self-harm, suicide, postnatal care problems whereas antipsychotic treatment may cause fetal exposure and related problems for fetus.

There is an increase of atypical antipsychotic drug use in pregnancy while the typical antipsychotic drug use has not been increased[3,4]. Since typical antipsychotics have side effects such as pre-term birth, low birth weight for gestational age, atypical antipsychotics have been preferred during pregnancy[5].

Due to their concentration, liposolubility, and molecular size, antipsychotics can enter fetal circulation through the placenta, and they can affect development and function of placenta[6-9]. They have the potency to antagonize fetal receptors. Serotonergic receptors found on rat embryo at embryonic day 15[10]. Antipsychotic drugs affect dopamine subtype D2 receptors and serotonin 5-HT2A receptors. There is not enough information about the blockade of dopamine receptors in the prenatal period by antipsychotics and its effect on neurological and behavioral development accordingly. Neurotransmitters are important for neural development so prenatal exposure to antipsychotics may affect neural development[11-13]. Singh et al. administered single dose ip haloperidol treatment to pregnant rats on gestation day 12 and it has been found out from their treatment that the hippocampal cortex of pups were less developed and poorly differentiated, moreover, the striatum was reduced in size[12]. Singh et al. showed that second generation antipsychotic quetiapine exposure may cause apoptotic neurodegeneration of fetal hippocampus[13]. It has been found out in another study related to this subject that antipsychotic drugs can alter neuroplasticity by over expression of dendritic protein genes[14]. Silva et al. demonstrated that dopamine antagonists may have a negative effect on spatial memory performance in rats[15].

Performances of males and females in Radial Arm Maze and Morris Water Maze have been tested and it has been found that males have advantages[16-18]. We do not have adequate information about the blockade of dopamine receptors in the prenatal period by antipsychotics and their effect on neurological or behavioral development, as well as the impact of gender differences on prenatal antipsychotic exposure. Healthcare providers are in need of more information about the side effects of prenatal antipsychotic exposure for deciding antipsychotic drug treatment during pregnancy. We tested one antipsychotic for each chemical class to compare the drug and gender differences: chlorpromazine (aliphatic phenothiazine derivative), thioridazine (piperidine phenothiazine derivative), fluphenazine (piperazine phenothiazine derivative), chlorprothixene (thioxanthene), haloperidol (butyrophenone), clozapine (benzepine), and sulpiride (benzamide derivative).

METHODS

Animals and treatments

Thirty-two female (200–220 g) and sixteen male (300–320 g) adult Sprague-Dawley rats were purchased from the laboratory animals unit of the Faculty of Medicine at Trakya University. All animals had access to water and food ad libitum and were housed with a 12-hour light cycle, 40-45% moisture, and at the temperature of 21°C±2°C. The experimental protocols were approved by the local Animal Care Ethics Committee. Four female and two male rats were grouped in cages for mating. Pregnant rats were detected and housed individually. Drugs were administered by intragastric gavage as water suspension shook before usage once a day during the gestation period until partition (from GD1 to GD 17–21). The following drugs were administered to pregnant rats: 1) 2 mg/kg haloperidol (H1512, Sigma–Aldrich, MO, USA); 2) 100 mg/kg thioridazine (Thioridazine hydrochloride, T9025, Sigma–Aldrich MO, USA); 3) 200 mg/kg sulpiride

(Sulpiride, S8010, Sigma–Aldrich MO, USA); 4) 20 mg/kg chlorprothixene (Chlorprothixene hydrochloride, C1671, Sigma–Aldrich MO, USA); 5) 40 mg/kg clozapine (Leponex, 100 mg tablet, Novartis, Istanbul, Turkey); 6) 10 mg/kg fluphenazine (Fluphenazine dihydrochloride, F4765, Sigma–Aldrich, MO, USA); and 7) 20 mg/kg chlorpromazine (Chlorpromazine hydrochloride, C8138, Sigma–Aldrich, MO, USA). There was also a control group that received water by intragastric gavage. Each group has 4 pregnant rats and there were total 32 pregnant rats and all pregnant gave birth and approximately half of the offspring were male and female. On the 25th postnatal day, offspring were grouped by their gender and drug exposure. 10 rats from each group were selected by random selection. There were male and female groups of 7 drug and control, so there were total 16 groups which have 10 rats for each group. All animals selected for this experiment (totally 160 rats) were kept alive until the end of the study.

Morris Water Maze

The Morris water maze was a 150 cm diameter, 60 cm deep circular pool filled with opaque water at 25°C±1°C, and water depth was 45 cm. There were external clues on the walls of the room. The pool was divided into four imaginary quadrants (NE, NW, SE, and SW). During the hidden platform test, an escape platform was placed 2 cm below the water surface at a certain position in the SW quadrant. Spatial learning was tested by hidden platform trial. In the probe test, the platform was removed from the pool. The swimming route of the animal in the pool was recorded by mounting a camera above the pool, and analyzed by Ethovision XT 7.0 (Noldus, Netherlands). Memory was tested by probe trial.

Procedure

The experiment involved two phases: the first one was the acquisition phase evaluated by a hidden platform test and the second one was retention phase by a probe test. Measure of learning is the

Table 1. Hidden platform test data of the control group: escape latency, thigmotaxis. (*: p<0.05, †: p<0.01, ‡: p<0.001, §: p<0.0001 were compared with the same day value of the same gender's control group; **: p<0.05, ††: p<0.01, ‡‡: p<0.001, §§: p<0.0001 were for males compared with females' value on the same day). (Repeated measures, two-way ANOVA, post-hoc Bonferroni test) (For each group, n=10) (The vertical lines represent the standard error of the mean).

	Block	Control		Haloperidol		Thioridazine		Sulpiride		Chlorprothixene		Clozapine		Fluphenazine		Chlorpromazine	
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Escape latency (sec)	1	60.0	60.0	58.1	53.7	51.5	51.7	56.2	56.5	51.6	58.6	51.3	59.6	57.0	58.7	57.9	59.0
	2	56.1	54.2	54.1	52.4	40.9§	45.4*	50.3	54.7	55.0	57.6	59.3	56.8	51.2	52.5	57.4	56.9
	3	48.0	44.9	51.5	49.3	40.6	47.5	49.1	53.9	51.8	46.1	53.1	47.9	44.9	53.2	52.5	58.4†
	4	35.7	37.4	49.8†	43.3	35.8	42.7	41.9	50.9†	49.9†	49.6*	55.1§,††	41.6	34.4§§	56.5§	44.4	49.9†
	5	22.8	25.3	48.6§	43.8§	29.5††	41.2§	42.0§	49.6§	45.1§	44.5§	51.8§,††	31.3*	24.7§§	48.0§	36.5‡	42.7§
Thigmotaxis (sec)	1	44.7	37.8	35.2*	37.1	28.3§	30.0*	34.6*	36.9	31.8‡	38.2	30.0‡	38.5	31.4§	34.8	36.2*	40.4
	2	35.5	28.6	33.2	28.8	18.8§	22.6	22.9	32.2	31.0	28.2	38.3	30.9	24.7†	25.0	31.0	36.8*
	3	22.6	23.1	29.2	22.6	17.9	23.1	28.8	32.6*	29.7**	20.5	32.9*	27.2	20.8**	30.0	30.3§	36.9§
	4	12.1	16.1	25.5‡	22.8	17.3	20.4	27.2§	29.8‡	29.0§,**	20.0	36.0§,‡‡	21.1	13.0§§	32.3§	20.4*	28.3‡
	5	7.5	9.0	20.4‡	21.5‡	13.4	19.6‡	23.9§	27.9§	23.8§	19.9†	34.8§,§§	18.8*	6.7§§	25.7§	17.0*	24.0§

escape latency which is the time spent to find the hidden location of escape platform. Thigmotaxis is the time spent on 10 cm perimeter of the walls of the pool.

The acquisition phase included four trials per day for five consecutive days. Different starting points were used at each trial (N, NW, S, and SE). Each time, the rat was placed somewhere in the pool that was close and facing the wall of the pool. When the rat found the platform, it was allowed to stay on the platform for 15 seconds. If the rat failed to find the platform in 60 seconds, it was guided to find the platform and forced to stay there for 15 seconds. At the end of the test, the rat was removed from the pool, dried off, and placed in its cage.

Twenty-four hours later, from the hidden platform test, the retention phase started. The platform was removed from the pool and each rat was released to the pool somewhere different (E) from former trials. After 60 seconds swimming, rat was removed from the pool.

Statistical Analysis

Statistical analyses were performed using repeated measures two-way ANOVA followed by the post hoc Bonferroni for comparisons with the control group or respective treatment groups in the hidden platform test and one-way ANOVA post hoc Bonferroni for the probe test (Graphpad Prism 6.0c for Mac OSX). A value of $p<0.05$ was considered statistically significant.

RESULTS

The results are presented in two parts as the hidden platform test and probe test.

For each group, average escape latency and thigmotaxis values in training are presented in Table 1.

In control male and female rats, a decreasing trend in escape latency showed that the female and male control groups learned the location of the platform (Figure 1). The thigmotaxis value showed a decrease progressively. There was no significant difference between the control male and female groups.

Data from the escape latency showed that learning was impaired in the haloperidol groups (Figure 2). In both genders, thigmotaxis increased compared to the values from the control animals.

In the thioridazine male group, escape latency decreased on the second day ($p<0.0001$) (Figure 3). Lower thigmotaxis was observed on the first two days in the thioridazine groups.

In the sulpiride groups, escape latency value was significantly higher on the fourth (for female $p<0.01$) and fifth days (for both $p<0.0001$) compared to the corresponding control groups (Figure 4). The sulpiride groups showed increased

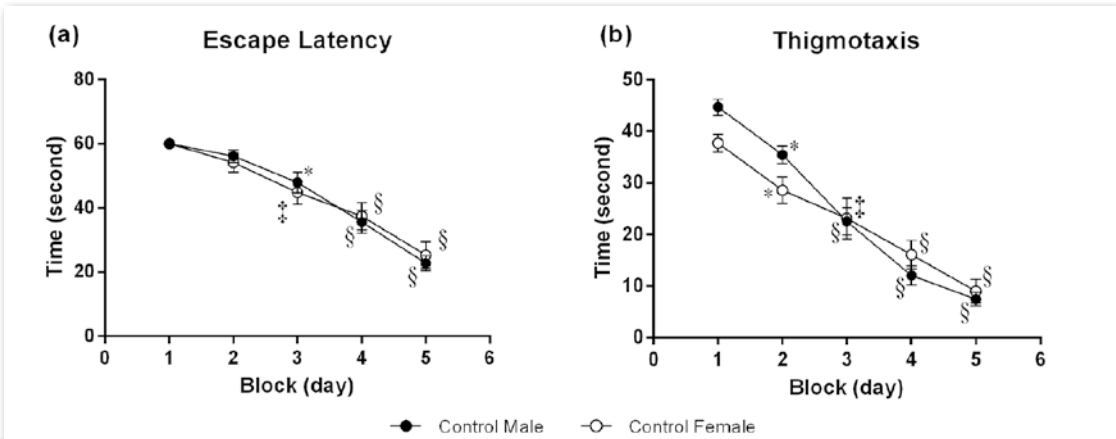

Figure 1: Hidden platform test data of the control group: (a) escape latency, (b) thigmotaxis. (*: $p<0.05$, ‡: $p<0.001$, §: $p<0.0001$ were compared with the first day value of the same gender). (Repeated measures, two-way ANOVA, post-hoc Bonferroni test) (For each group, n=10) (The vertical lines represent the standard error of the mean).

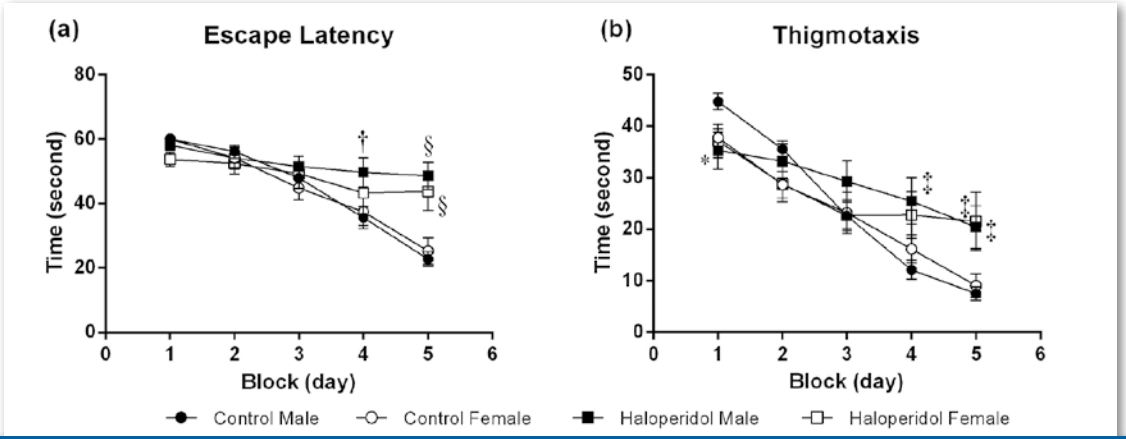

Figure 2: Hidden platform test data of the haloperidol group. (a) escape latency, (b) thigmotaxis. (*: p<0.05, †: p<0.01, ‡: p<0.001, §: p<0.0001 were compared with the same day value of the same gender's control group) (Repeated measures, two-way ANOVA, post-hoc Bonferroni test) (For each group, n=10) (The vertical lines represent the standard error of the mean).

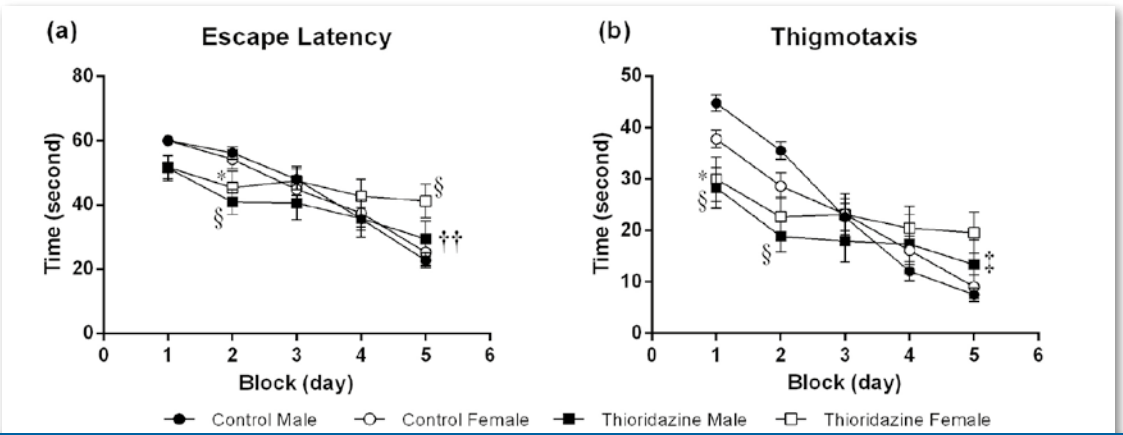

Figure 3: Hidden platform test data of the thioridazine group. (a) escape latency, (b) thigmotaxis. (*: p<0.05, ‡: p<0.001, §: p<0.0001 were compared with the same day value of the same gender's control group; ††: p<0.01 was for males compared with females' value on the same day) (Repeated measures, two-way ANOVA, post-hoc Bonferroni test) (For each group, n=10) (The vertical lines represent the standard error of the mean).

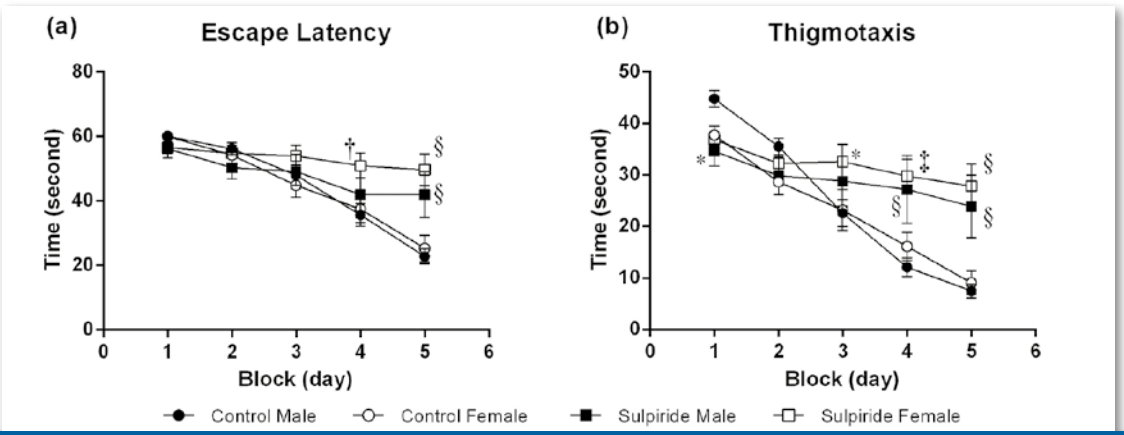

Figure 4: Hidden platform test data of the sulpiride group. (a) escape latency, (b) thigmotaxis. (*: p<0.05, †: p<0.01, ‡: p<0.001, §: p<0.0001 were compared with the same day value of the same gender's control group) (Repeated measures, two-way ANOVA, post-hoc Bonferroni test) (For each group, n=10) (The vertical lines represent the standard error of the mean).

thigmotaxis compared to the control groups.

Both of the chlorprothixene groups had significant increases in escape latency on the fourth (for male p<0.01, for female p<0.05) and fifth days (for both p<0.0001), which signifies disrupted learning (Figure 5). Changes in the learning parameters with chlorprothixene were parallel to the ones in thigmotaxis. It has been observed that thigmotaxis increased in both of the chlorprothixene groups when compared to the control groups.

Escape latency for the clozapine male group was higher on the fourth (p<0.0001) and fifth days (p<0.0001) compared to the male control (Figure 6). Similar changes in thigmotaxis parameters were observed in the clozapine male group.

Female fluphenazine group has a higher latency value for escaping on the fourth (p<0.0001) and fifth (p<0.0001) days compared to the female control group (Figure 7). Similar changes in thigmotaxis parameters were observed in the fluphenazine female group.

Escape latency value was higher in both chlorpromazine groups compared to the corresponding controls (Figure 8). Thigmotaxis increased in the chlorpromazine groups.

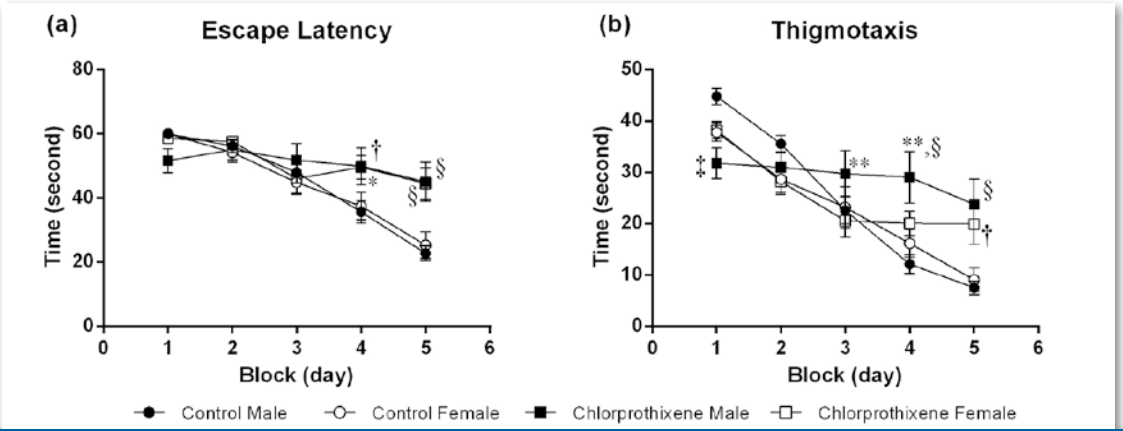

Figure 5: Hidden platform test data of the chlorprothixene group. (a) escape latency, (b) thigmotaxis. (*: p<0.05, †: p<0.01, ‡: p<0.001, §: p<0.0001 were compared with the same day value of the same gender's control group; **: p<0.05 was for males compared with females' value on the same day) (Repeated measures, two-way ANOVA, post-hoc Bonferroni test) (For each group, n=10) (The vertical lines represent the standard error of the mean).

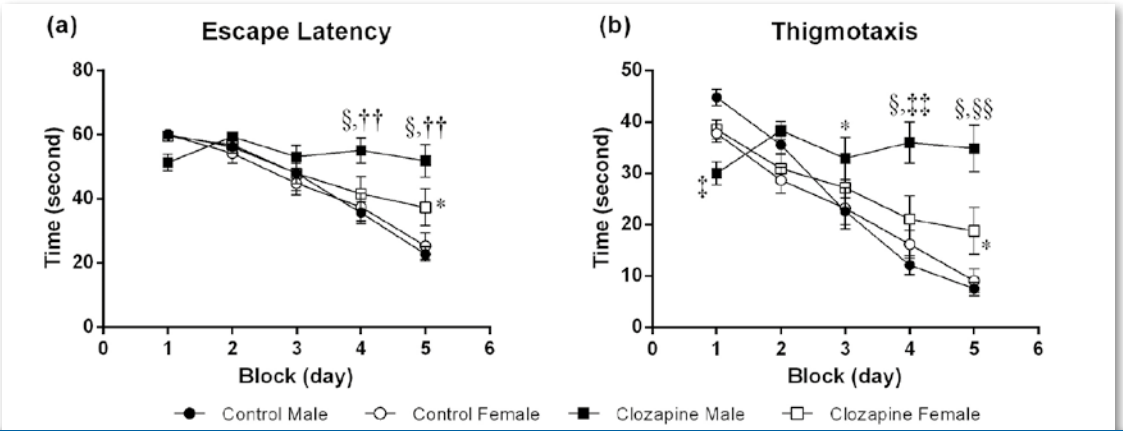

Figure 6: Hidden platform test data of the clozapine group. (a) escape latency, (b) thigmotaxis. (*: p<0.05, ‡: p<0.001, §: p<0.0001 were compared with the same day value of the same gender's control group; ††: p<0.01, ‡‡: p<0.001, §§: p<0.0001 were for males compared with females' value on the same day) (Repeated measures, two-way ANOVA, post-hoc Bonferroni test) (For each group, n=10) (The vertical lines represent the standard error of the mean).

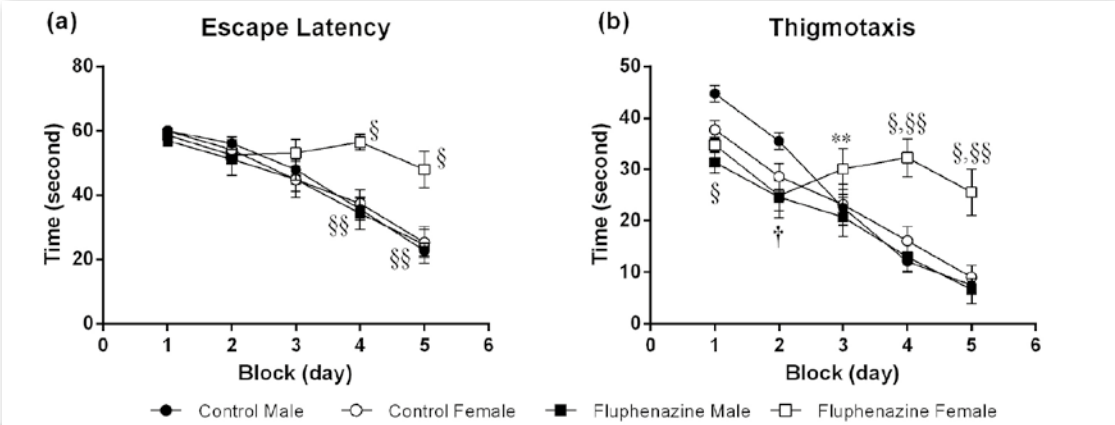

Figure 7: Hidden platform test data of the fluphenazine group. (a) escape latency, (b) thigmotaxis. (†: p<0.01, §: p<0.0001 were compared with the same day value of the same gender's control group; **: p<0.05, §§: p<0.0001 were for males compared with females' value on the same day) (Repeated measures, two-way ANOVA, post-hoc Bonferroni test) (For each group, n=10) (The vertical lines represent the standard error of the mean).

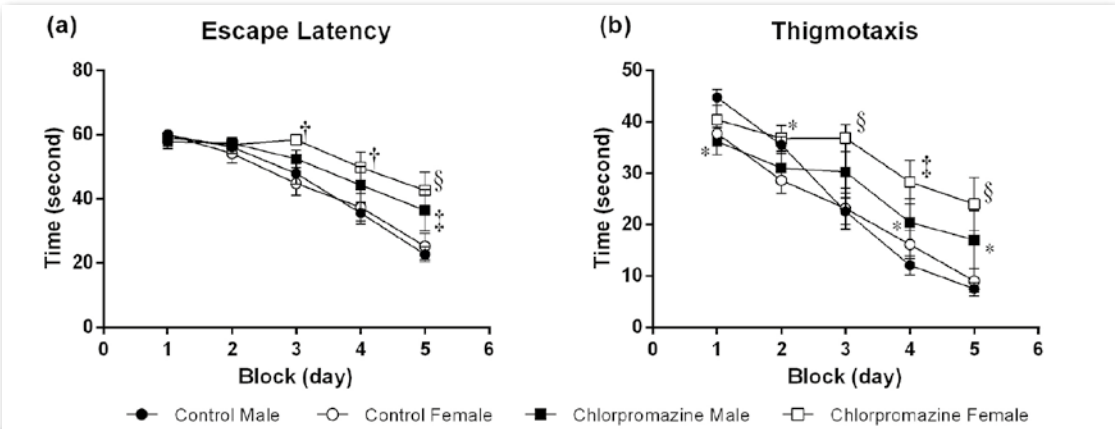

Figure 8: Hidden platform test data of the chlorpromazine group. (a) escape latency, (b) thigmotaxis. (*: p<0.05, †: p<0.01, ‡: p<0.001, §: p<0.0001 were compared with the same day value of the same gender's control group) (Repeated measures, two-way ANOVA, post-hoc Bonferroni test) (For each group, n=10) (The vertical lines represent the standard error of the mean).

Probe Test Results

There were no statistically significant differences among groups with respect to time spent in the target quadrant (SW) (Figure 9), and Thigmotaxis on probe test (Figure 10).

DISCUSSION

The results of our study show that prenatal exposure to antipsychotics increased the latency for escaping in all groups except for the male groups given fluphenazine and thioridazine. However, the rats in these groups showed more thigmotaxis compared to the control groups. Thigmotaxis indicates that the animal has impairment in the realization of the hidden platform task. Therefore, learning impairment that we observed may be due to inability of the animal to solve the problem rather than a specific learning impairment.

The deterioration of learning performance that we found is consistent with previous studies[12,19]. Rosengarten applied 2 mg/kg/day haloperidol with 0.1% saccharin added to drinking water on gestation days 8 to 18 and found impaired learning and memory by the radial arm maze test[19]. Singh and Singh intraperitoneally injected 50 mg/kg haloperidol to pregnant Charles Foster rats on gestation day 12 and they found that prenatal

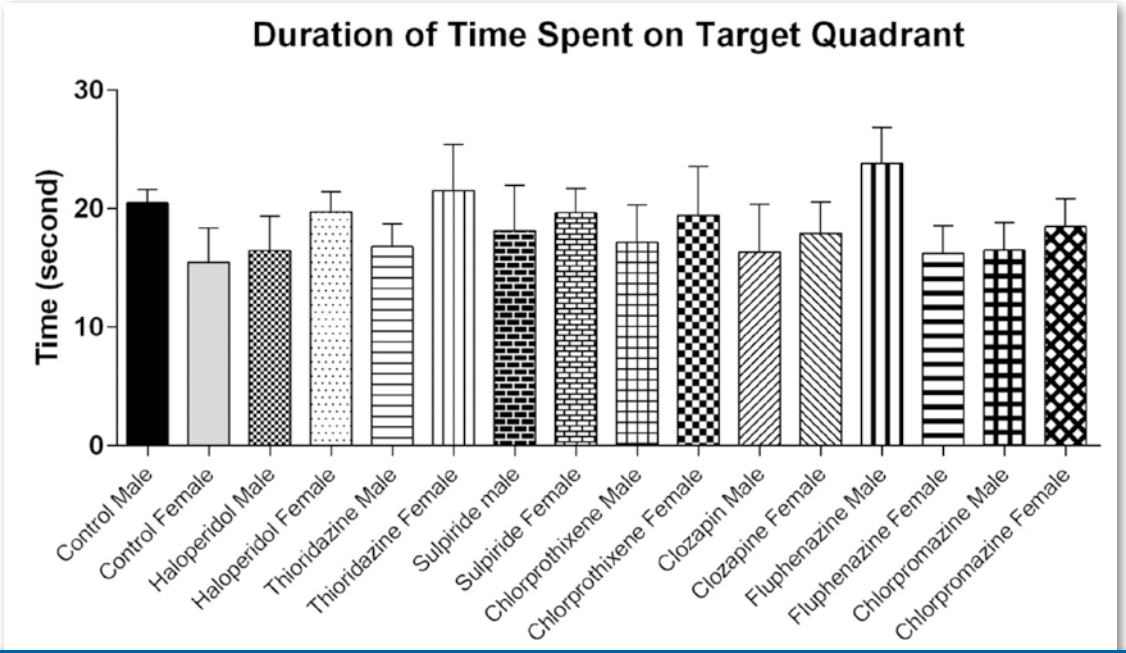

Figure 9: Duration of time spent in the target quadrant. (One-way ANOVA, post-hoc Bonferroni test) (For each group, n=10) (The vertical lines represent the standard error of the mean.)

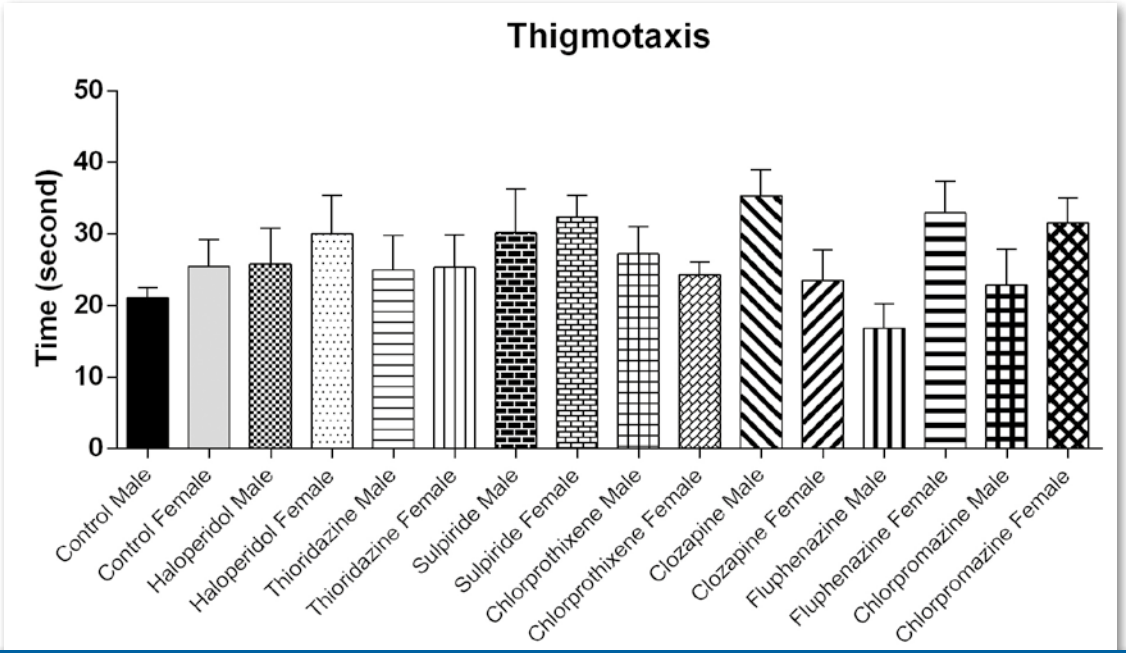

Figure 10: Thigmotaxis. (One-way ANOVA, post-hoc Bonferroni test) (For each group, n=10) (The vertical lines represent the standard error of the mean.)

haloperidol exposure led to impairment in learning on passive avoidance test[12].

In contrast to our study, Zuo et al. reported that prenatal exposure to sulpiride had no effect on learning and memory in the Morris water maze hidden platform test and they suggested that this prenatal administration of sulpiride does not affect neither learning in the hidden platform test nor memory in the probe test[20]. This discrepancy of their test with our finding can be explained with

methodological differences. They treated pregnant rats with 200 mg/kg/day sulpiride and 0.1% saccharine by adding them to the drinking water on days from 6 to 18 of gestation. Furthermore, they had applied habituation swimming for 180 sec/day without a platform for two days before the experiment. This training practice may lead thigmotaxis to decrease so that this may explain the difference between their and our results.

Singh and Singh injected haloperidol to pregnant rats (2.5 mg/kg i.p. gestation day 12–20) and the offspring showed anxiogenic behavior on tests when they were eight weeks old[21]. The high thigmotaxis that we obtained from our trial is a sign of anxiety and may support the results Singh and Singh[21].

One of the challenges we have encountered that we searched but could not find any reported data about the effects of prenatal chlorpromazine, clozapine, fluphenazine, thioridazine, and chlorprothixene exposure on spatial learning and memory. Our study will pioneer further studies.

Metabolism, distribution, and elimination rates of animals are different from the ones of humans so it is difficult to infer exact results from animals for humans, but that animals have standard nutrition during pregnancy and from offspring to adulthood, and animals did not take substances other than protocol during experimental time as well in our study has provided advantages when compared with the human study.

We were unable to locate any reported data about the effects of prenatal antipsychotic drug exposures on learning and memory of adult rats. Peng et al. reported that fetal exposure to atypical antipsychotics (clozapine, risperidone, sulpiride, olanzapine, and quetiapine) may cause short-term delayed development in cognitive, motor, social–emotional, and adaptive behavior in infants but this was a human study, and subjects were neither tested neither in adult period nor for specific to spatial learning and memory[25].

Limitations of our study are as follows: before Morris water maze tests, open field test could be done for validating anxiety signed by high thigmotaxis. Further research is needed for prenatal antipsychotic exposure and anxiety relation. Before prescribing antipsychotics this effect should be take into account. Different doses of drugs could be applied, but we preferred seven drugs one dose for comparing drugs and genders. There were 16 groups; working with more was not practical. Since some drugs were insoluble in water for standardization of drug treatment, we applied with intragastric gavage as water suspension.

There have been no systematic studies about exposure to prenatal antipsychotics in relation to learning and memory in the literature, so as far as we know this is the first systematic study that revealed the effect of prenatal antipsychotic exposure on learning and memory in adult rats. Moreover, there are no reports about prenatal exposure to chlorpromazine, clozapine, fluphenazine, thioridazine, and chlorprothixene on spatial learning and memory and this study would fill that information gap in the literature. In this present study, the effect of prenatal exposure to antipsychotics from seven different classes on spatial learning and memory in adulthood was examined with Morris water maze tests by comparing drug groups and gender differences. We used five parameters for the hidden platform test and two parameters for the probe test to support the reliability of the test results. In order to limit the article length, we did not present other data (total distance, swimming speed, mean distance to platform values on trial test and latency to reach target quadrant, times spent on quadrants, average distance to platforms location, and swimming speed on probe test), however, in short, they are in parallel to the parameters presented here.

CONCLUSIONS

In general, rats exposed to antipsychotics in the prenatal period demonstrated deterioration in learning in the Morris water maze task; however, these rats also showed an increase in thigmotaxis. Taking these effects into consideration together, we concluded that prenatal antipsychotic exposure may negatively affect the problem with solving ability of animals rather than specifically affecting the learning process.

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