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ORIGINAL RESEARCH

Effects of Prenatal and Lactational Vortioxetine Exposure on Emotional States, Motor Activities and Cognitive Performances of Offspring

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Abstract

Objective: Pregnancy and breastfeeding are periods when hormonal fluctuations in women are intense and the risk of mood disorders is high. Uncured psychiatric disorders reduces the mother's quality of life on the one hand and harms the developing fetus on the other. The inability of mothers with psychiatric problems to provide the necessary care to their babies after birth and during the lactational period is another risk factor for the baby. For this reasons, the prescription of antidepressants to pregnant women has become increasingly common in recent years. On the other hand, studies indicate that exposure to antidepressants in the early stages of life causes some negative effects on the neurodevelopmental process of the fetus. Hence, it is of clinical importance to clarify the risks caused by the use of antidepressants during pregnancy. Therefore, it was aimed to investigate potential effects of prenatal and lactational exposure to vortioxetine, which is a relatively new antidepressant with a multimodal mechanism of action, on the emotional states, motor behaviors and cognitive performances of the offspring, in this study.

Methods: Vortioxetine was administered orally to adult Sprague Dawley female rats at doses of 10 and 20 mg/kg/day before conception and continuing until the pups were weaned (P21). Behavioral experiments were performed with 90-day-old (P90) adult offspring. Motor activity, anxiety, depression and cognitive performance parameters of the rats were assessed using activity-meter, elevated plus-maze, modified forced swimming and passive avoidance tests, respectively.

Results: Data from activity-meter tests revealed that prenatal and lactational exposure to vortioxetine (20 mg/kg) resulted in significant increases in horizontal, ambulatory, and stereotypic activity counts and walking distance values of the offspring, suggesting that vortioxetine exposure induced hyperactivity in these animals. In contrast, early-life vortioxetine exposure did not alter the number of vertical movements, indicative of exploratory behavior in rats. This finding, together with data showing that the offspring's preference for the open arm in elevated plus-maze tests was reduced, pointed out that these animals had increased anxiety levels. When the findings of the modified forced swimming tests were examined, it was detected that the duration of active swimming and climbing behaviors of rats increased and the immobility period shortened. These findings are thought to be related to an increase in the motor activity of the offspring rather than a decrease in the animals' depressive behavior. In the passive avoidance tests, it was observed that vortioxetine exposure did not cause any significant changes in the emotional learning and memory performances of the offspring.

Conclusion: The findings obtained in this study showed that maternal exposure to vortioxetine, especially at high doses, may not be safe for the baby and suggested that this drug may not be superior to other antidepressants in terms of use at prenatal and lactational periods. On the other hand, comprehensive clinical studies are needed on children of mothers who used this drug before birth and during breastfeeding to gain a clearer understanding of the short – and long-term effects of early-life vortioxetine exposure on children.

Keywords: Anxiety, Cognition, Depression, Motor activity, Prenatal and lactational exposure, Vortioxetine

INTRODUCTION

Hormonal fluctuations experienced in women, especially during pregnancy and the postpartum period, are known to increase risk of depressive disorders (1). One of the most critical risk factor for perinatal depression is a pre-existing history of depression in the patient. In such cases, discontinuing antidepressant use may not be recommended as it may pose a risk for both the mother and the baby (2). Besides, increased stress during pregnancy is also a major risk for the development of postpartum depression. It has been reported that

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daughters of mothers with postpartum depression are at higher risk for depressive disorders (3), while sons are at higher risk for antisocial behavior disorders (4).

It is known that both depression itself and the medications used in its treatment have various effects on fetal development. This situation forces clinicians to choose between exposing the fetus to antidepressants during pregnancy and leaving the mother and fetus with the risks of untreated maternal depression. Data from clinical studies indicate that the use of antidepressants during pregnancy and breastfeeding has continued to increase in the last decade (5).

It has been reported that the most commonly prescribed antidepressants during pregnancy are selective serotonin reuptake inhibitors (SSRIs) (5, 6). Although SSRIs are assumed to be relatively safe for both mother and baby, it is known that these drugs can cross the placental barrier and reach the developing fetus. Moreover preclinical studies have shown that rats exposed to SRRI drugs during the neonatal period exhibit long-term neurobiological deficits in adulthood (7). For example, it has been observed that offspring exposed to fluoxetine in-utero and early postnatal periods have permanent changes in emotional behavior and brain neuroplasticity when they reach adulthood (8-10). There are also clinical studies in the literature with results parallel to these findings. For example, SSRI exposure during the perinatal period has been shown to cause various neurodevelopmental deficits in brain and behavioral alterations in children (11-13). Negative effect on cognitive performance (14) as well as decreased IQ scores (15) have been reported for the children exposed to SSRI (fluoxetine) in their prenatal period. Moreover, numerous studies have associated prenatal SSRI exposure with an increased risk of autism spectrum (16-19) and attention deficit hyperactivity disorders (20).

Vortioxetine is a drug licensed for use in the treatment of major depressive disorder in adults under the trade names such as Brintellix®, Trintellix® and Fonksera®. In vitro studies conducted to elucidate the mechanism of action of vortioxetine have shown that this drug is an antagonist on serotonergic 5-HT_3, 5-HT_7 and 5-HT_{1D} receptors; a partial agonist on the 5-HT_{1B} receptor; an agonist on the 5-HT_{1A} receptor, and has inhibitory properties for the serotonin transporter (21). It can be hypothesized that maternal exposure to this drug, which has widespread effects on the serotonergic system of the brain, may cause changes in emotional state and cognitive performance of the offspring similar to SSRIs. Given that vortioxetine affects the serotonergic system through multiple mechanisms different from SSRIs that primarily block reuptake, it is possible that it may cause more dramatic effects on fetal neurodevelopment. Despite this, there are very few studies in the literature on the effects of maternal vortioxetine exposure on brain development or emotional behavior of the offspring (22, 23). Therefore, this study aimed to investigate the emotional states as well as motor and cognitive performances of offspring exposed to vortioxetine during the prenatal and lactation periods.

METHODS

Animals

Adult female and male Sprague Dawley rats of the same age, weighing 250-300 g, were used for the study. Rats were housed in Anadolu University Research Unit for Experimental Animals, under standard temperature (24 ± 1 °C), ventilation and humidity conditions with a 12-hour light, 12-hour dark cycle.

Drugs

Vortioxetine hydrobromide (Sigma, St. Louis, MO, USA) was orally administered to adult female rats at daily doses of 10 mg/kg and 20 mg/kg (24, 25) starting 3 weeks before conception, throughout pregnancy and until weaning (P21) after birth (26). Three weeks after the start of vortioxetine treatment, adult male rats were placed in the female cages for mating. Successful mating was confirmed by the presence of sperm in vaginal lavage performed daily during the first two hours of the light cycle. Following mating was confirmed, the male was removed from the breeding cage.

Behavioral Tests

After birth, the pups were not disturbed except for routine cage changes until they were weaned on day 21. On P21, randomly selected male offspring were divided into experimental groups of 10 animals each. Behavioral tests were started on day 90 (P90) (27).

Activity-meter Test

Probable alterations in the motor activity parameters of the rats were evaluated using an activity-meter device (Commat, ACT508, Ankara, Turkey) consisting of a plexiglass cage (base size 40x40 cm) equipped with IR sensors. The horizontal, vertical, stereotypic, ambulatory activities and walking distance values of the rat placed

in the middle of the device were recorded for a period of 10 minutes (28). After each measurement, the device was cleaned with ethanol.

Elevated Plus-maze Test

The elevated plus-maze test was used to measure anxiety levels of animals as described previously (29). The apparatus used in this study is a plus-shaped maze consisting of two open and two closed arms and a central region where they meet. The method is based on the fact that walking in the open arms and being elevated from the ground triggers anxiety in animals. During the 10-minute measurement period, the number of times the animals entered the open and closed arms and the time they spent in these arms were recorded. Percentage of open arms entries (POAE) and percentage of time spent in open arms (PTOA) were considered as criteria to determine the level of anxiety.

Modified Forced Swimming Test

The modified forced swimming test modified by Detke from Porsolt (30) was used to assess depression levels of animals, as described previously. The apparatus is a plastic cylinder with a height of 50 cm and a diameter of 30 cm. In the first (training) phase of the experiments, rats were made to swim for 15 min to adapt to the apparatus. 24 h after training, rats were put back into the water for the second (test) phase. Periods of immobility, climbing, and swimming longer than 5 s were recorded with a 5-min stopwatch (31).

Passive Avoidance Test

Fear-conditioned emotional memory was assessed by using a passive avoidance device as described previously (Ugo Basile model 7551, Italy) (32). The device consists of two separate compartments, light and dark, each measuring 22 cm x 21 cm x 22 cm. The illuminated white compartment was connected to a dark compartment with a grid floor capable of applying electric current (0.5 mA). The unavoidable electric current was applied to the feet of the experimental animal via a shock generator. The compartments were separated by a flat partition on the floor with an automatically operated sliding door.

At the beginning of the experiment, rats were given a training trial. They were placed in the light compartment for 30 s, then the door between the compartments was opened, allowing them to move freely to the dark compartment. An acquisition trial was performed 15 min later, the animal was placed back in the light compartment, and after a 30 s acclimation period, the door between the compartments was opened. The time to move to the dark compartment was recorded as the training latency (TL). If the animal failed to enter the dark compartment within 300 seconds, it was eliminated from the experiment.

Once the animal had completely entered the dark compartment, the door between the compartments was automatically closed and a 0.5 mA electric shock (lasting 3 seconds) was applied to the animal's feet through the cage floor. The animal was then removed from the apparatus and placed in its cage. A memory trial was administered 24 hours after the acquisition trial. No electric shock was administered during this trial and the time taken to enter the dark compartment was recorded as the second transition latency (STL). The cut-off time was set at 300 seconds. Each compartment was cleaned to remove possible odor clues between each trials.

Statistical Analysis

GraphPad Prism 8.4.3 (GraphPad Software, San Diego, CA, USA) program was used for the statistical analysis. Experimental data were analyzed by one-way analysis of variance (ANOVA) and Tukey's multiple comparison test was applied for comparisons between groups. Experimental results were given as mean ± standard error of the mean (SEM) and $P<0.05$ was considered significant.

RESULTS

Findings of the Activity-meter Measurements

Effect of prenatal and lactational vortioxetine administrations on horizontal and vertical activity numbers of the offspring were presented in Figure 1. Results of the ANOVA tests revealed that horizontal activities of animals exposure to vortioxetine at 20 mg/kg dose were significantly higher than control group [$F (2, 27) = 3.45$, $p < 0.05$]. On the other hand, no significant change was observed in the horizontal movement numbers of rats exposed to vortioxetine at a dose of 10 mg/kg (Fig. 1A). In addition, early-life vortioxetine exposure did not cause a significant change in the vertical movement numbers of rats [$F (2, 27) = 0.09$, $p > 0.05$] (Fig. 1B).

Figure 2 shows the prenatal and lactational vortioxetine exposure-induced alterations in the ambulatory activity [$F (2, 27) = 3.54$, $p < 0.05$] (Fig. 2A) and walking distance [$F (2, 27) = 3.80$, $p < 0.05$] (Fig. 2B) parameters of the offspring. ANOVA tests results indicated that both of

these parameters were significantly higher in 20 mg/kg vortioxetine administrated animals compared to the control animals. On the other hand, 10 mg/kg vortioxetine dose did not cause an increase in ambulatory activities and walking distances of rats similar to the 20 mg/kg dose.

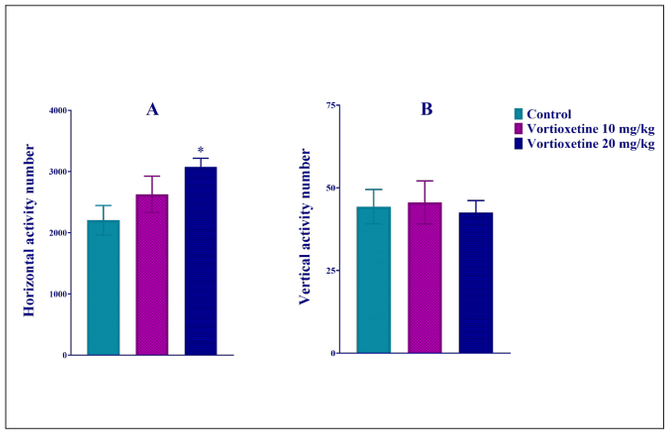

Figure 1. Effects of early-life vortioxetine exposure (10 and 20 mg/kg/day) on horizontal (A) and vertical (B) activity numbers recorded in the activity-meter test of adult male offspring. Significant difference compared to the control group *p < 0.05. One-way ANOVA, post hoc Tukey HSD, n=10.

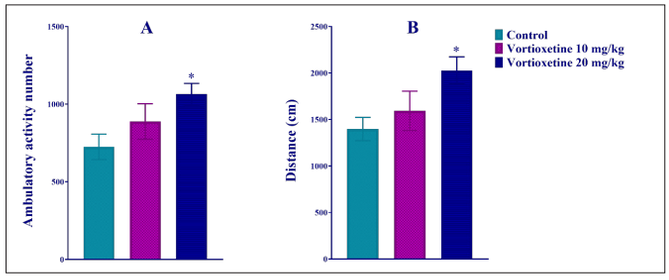

Figure 2. Effects of early-life vortioxetine exposure (10 and 20 mg/kg/day) on ambulatory activity numbers (A) and walking distance values (B) recorded in the activity-meter test of adult male offspring. Significant difference compared to the control group *p < 0.05. One-way ANOVA, post hoc Tukey HSD, n=10.

Changes caused by vortioxetine exposure on the stereotypic activities of the offspring are shown in Figure 3. While the 20 mg/kg dose increased the stereotypic activities of rats, the 10 mg/kg dose did not cause a statistically significant difference [F (2, 27) = 4.12, p < 0.05].

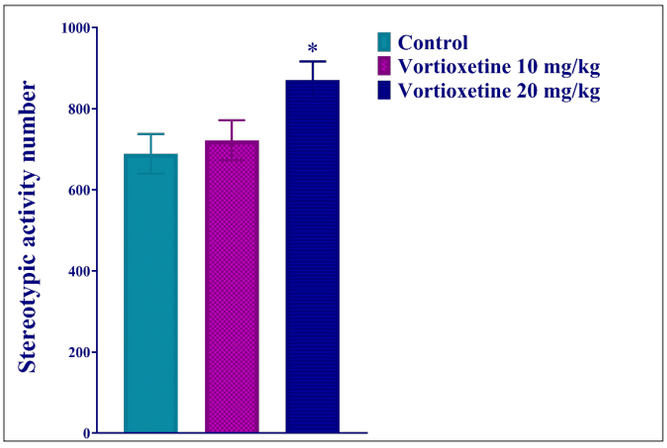

Figure 3. Effects of early-life vortioxetine exposure (10 and 20 mg/kg/day) on stereotypic activity numbers recorded in the activity-meter test of adult male offspring. Significant difference compared to the control group *p < 0.05. One-way ANOVA, post hoc Tukey HSD, n=10.

Findings of the Elevated Plus-maze Tests

Effect of prenatal and lactational vortioxetine administrations on anxiety parameters of the offspring were presented in Figure 4. The data obtained from ANOVA analysis exhibited that vortioxetine administrations at 20 mg/kg dose significantly reduced the calculated POAE [F (2, 27) = 3.60, p < 0.05] (Fig. 4A) and PTOA values [F (2, 27) = 3.55, p < 0.05] (Fig. 4B). On the other hand, vortioxetine was ineffective at a dose of 10 mg/kg.

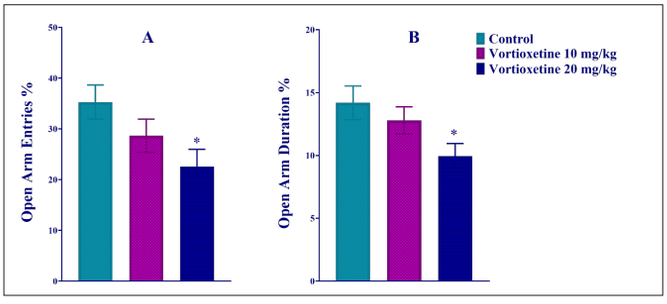

Figure 4. Effects of early-life vortioxetine exposure (10 and 20 mg/kg/day) on calculated open arm entries % (A) and open arm duration % values (B) in the elevated plus-maze test of adult male offspring. Significant difference compared to the control group *p < 0.05. One-way ANOVA, post hoc Tukey HSD, n=10.

Findings of the Modified Forced Swimming Tests

Figure 5 shows the changes caused by prenatal and lactational vortioxetine exposure on swimming [F (2, 27) = 4.00, p < 0.05] (Fig. 5A), climbing [F (2, 27) = 3.62, p < 0.05] (Fig. 5B) and immobility [F (2, 27) = 4.28, p < 0.05] (Fig. 5C) time values of the offspring. The results obtained from ANOVA analysis showed that animals exposed to vortioxetine at 20 mg/kg dose had longer swimming and climbing times and shorter immobility durations than the corresponding control groups. Vortioxetine at 10 mg/kg dose did not cause a statistically significant change.

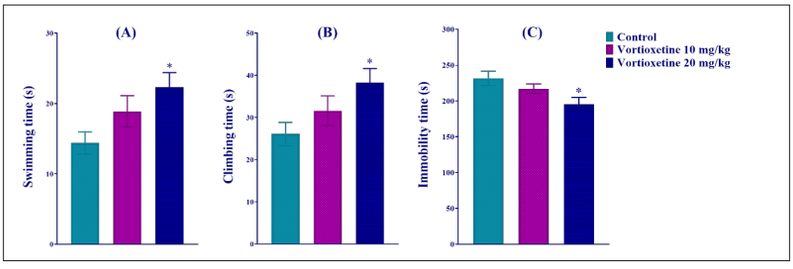

Figure 5. Effects of early-life vortioxetine exposure (10 and 20 mg/kg/day) on swimming (A), climbing (B) and immobility times (C) recorded in the modified forced swimming test of adult male offspring. Significant difference compared to the control group *p < 0.05. One-way ANOVA, post hoc Tukey HSD, n=10.

Findings of the Passive Avoidance Tests

Effects of prenatal and lactational vortioxetine exposure on the TL [F (2, 27) = 0.63, p > 0.05] and STL [F (2, 27) = 0.61, p > 0.05] values of the offspring recorded in the passive avoidance device are shown in Figure 6. Administration of 10 mg/kg or 20 mg/kg doses of vortioxetine did not cause any significant change in TL or STL values of the offspring.

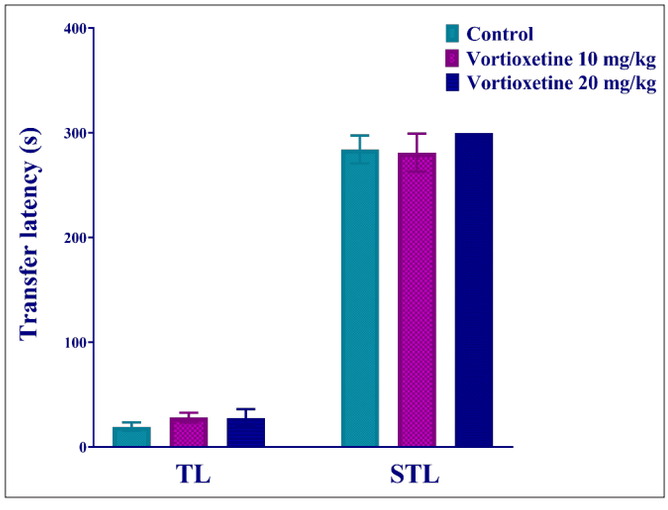

Figure 6. Effects of early-life vortioxetine exposure (10 and 20 mg/kg/day) on transfer latency values recorded in the passive avoidance test of adult male offspring. One-way ANOVA, post hoc Tukey HSD, n=10.

DISCUSSION

Based on studies reporting that early-life antidepressant exposure has harmful effects on pups (11-15, 17), this study aimed to investigate the changes that may occur in the emotional states, motor behaviors and cognitive performances of offspring exposed to the antidepressant drug vortioxetine during prenatal and lactational periods.

Possible behavioral changes in the offspring were evaluated using activity-meter, plus-maze and modified forced swimming tests. Activity-meter test is a method used to measure the spontaneous movements of experimental animals for a pre-determined period (28). In this test, the device automatically records information such as the locomotor activities of the experimental animal in horizontal and vertical directions, the number of ambulatory movements and the walking distance values. Another important parameter measured in activity-meter tests is stereotypic activity of the animal. In this study, data obtained from activity-meter tests revealed that horizontal locomotor activities of offspring exposed to vortioxetine during the prenatal and lactational periods were robustly higher than the control group. In addition, the number of ambulatory movements of the offspring as well as the distance they travelled in the cage increased significantly compared to the control rats that were not treated with the drug. The increase in horizontal activity, ambulatory movements

and distance covered in the cage of the offspring are the findings that support each other and show that locomotor hyperactivity has developed in these animals (33). It is known that the development of a hyperactive behavior profile is predominantly associated with the increase in the dopaminergic activity in the central nervous system (34, 35). On the other hand, changes in the functions of other neurotransmitters such as glutamate, GABA, acetylcholine, and serotonin may also have altered the locomotor activity of the experimental animals (36).

The activity-meter test data also revealed that stereotypic activity increased significantly compared to the control group. The increase in the number of stereotypic movements of the offspring was another finding suggesting the strengthening of dopaminergic neurotransmission (35, 37, 38). Determining the levels of neuromediators (especially dopamine) that regulate motor activity in the relevant brain regions of the offspring using reliable analytical methods will contribute to the elucidation of the mechanisms underlying the motor activity changes revealed in this study.

Another finding obtained from the activity-meter tests is that, unlike the horizontal activity numbers, no significant change was observed in the vertical activity counts of the offspring exposed to vortioxetine during the prenatal and lactational periods. This may be due to the animals preferring to exhibit stereotypic behavior in their current position rather than moving in vertical direction. Another possible explanation is that the animals' high anxiety levels may have suppressed vertical movements, which are known to be associated with exploratory behavior and are influenced by the animals' emotional state (39). To clarify this possibility, the anxiety levels of offspring exposed to vortioxetine during early-life were also evaluated in this study.

The plus-maze test is a highly valid and reliable method used to evaluate anxiety-related behaviors in experimental animals (29, 40). In this study, results of the plus-maze test indicated that POAE and PTOA values of the offspring exposed to vortioxetine in the prenatal and lactational periods were significantly lower than the offspring in the control group. These data revealed that the offspring exposed to vortioxetine did not prefer to enter to the open arm of the apparatus and/or spend time there. These findings indicated that vortioxetine exposure caused an increase in the anxiety levels of the offspring and supported our prediction that the decreased number of vertical activity observed in the activity-meter tests might be related to high anxiety levels of these animals.

Another method used in this study to investigate the effects of early-life vortioxetine exposure on the emotional state of the offspring is the modified forced swimming test. In this test, which is a modified form of Porsolt's classical forced swimming test, the depth of the apparatus is increased so that the active escape behaviors of the rodents (climbing and swimming) can be observed and assessed (31). In this study, obtained data showed that both swimming and climbing times of the offspring exposed to vortioxetine during the prenatal and lactational periods were significantly increased compared to the control group, while their immobility time were shortened. Generally, in modified forced swimming tests, the shortening of the immobility periods of the rats and the prolongation of the durations of their escape-oriented active behaviors are considered as antidepressant-like effects. Therefore, these data may at first glance be interpreted as early-life vortioxetine exposure causing an antidepressant-like effect in experimental animals. On the other hand, when conditions that cause hyperactivity in experimental animals are present, as in this study (Figures 1 and 2), it is known that false positive results can be obtained in such depressive behavior screening tests (41). In this context, it should be noted that the anti-immobility effect observed in the modified forced swimming test may be due to the increased motor performances of the animals and it should not be directly attributed to an antidepressant-like effect. Therefore, to assess the effects of early-life vortioxetine exposure on the emotional state of offspring, it is necessary to use different testing methods in which alteration in the animals' motor performance is not a serious confounding factor.

When the findings of the activity-meter, elevated plus maze, and modified forced swimming tests were evaluated together, it was seen that the behavioral changes in the offspring exposed to 20 mg/kg vortioxetine were not caused by exposure to 10 mg/kg dose of vortioxetine. This suggests that behavioral alterations triggered by vortioxetine exposure in early-life occur in a dose-dependent manner and that use of this drug, especially at high doses, may pose a risk to the offspring.

There is only one study in the literature (23) regarding the effects of prenatal vortioxetine exposure on the emotional behaviors of the offspring. In the mentioned study, vortioxetine was administered to Wistar rats at doses of 1 and 2 mg per day (p.o.) between days 6 and 21 of pregnancy. Depression and anxiety behaviors of

the offspring were evaluated in experiments conducted between days 56 and 70 after birth. The authors suggested that prenatal exposure to vortioxetine altered the emotional states of both male and female offspring and that these changes were due to reductions in serotonin, dopamine, and noradrenaline levels in the animals' prefrontal cortex. (23). The common points between the results of this paper and our study are that vortioxetine exposure increased ambulatory activities and anxiety levels of the offspring in both studies. On the other hand, in the study of Singh and co-workers, unlike ours, vortioxetine exposure decreased vertical activity and self-grooming in the offspring and caused depression-like behavior in them. The reasons why the results of our study differ from the previous report may be as follows: a) vortioxetine was started to be administered 3 weeks before pregnancy b) vortioxetine was given at daily doses of 10 and 20 mg/kg c) the offspring were also exposed to the drug during the lactational period d) the offspring were taken into the experiment at P90 and e) different animal strain was used in our study.

In the scope of this study, the effects of early-life vortioxetine exposure on the cognitive performance of the offspring were evaluated with a passive avoidance test. This is a method frequently preferred in rodent emotional memory studies (32, 42). The results obtained in this study revealed that the offspring exposed to vortioxetine remembered the electric shock experience they had in the dark field similarly to the rats in the control group. This finding suggest that the cognitive performance of the offspring was not impaired. However, it is known that learning and memory have different dimensions and these differences should be further evaluated by suitable and reliable tests (42, 43). In other words, in order to be able to say that early-life vortioxetine exposure does not cause any changes in the cognitive performance of the offspring, the learning and memory performances of these animals should also be evaluated with other methods such as Morris water maze tests (spatial learning) or novel object tests (recognition memory) etc.

In summary, results of this study revealed that prenatal and lactational exposure to the multimodal antidepressant vortioxetine causes locomotor hyperactivity, increased stereotypic behavior and high anxiety levels in the offspring. These alterations indicate that early-life vortioxetine exposure alters normal physiological functioning in brain regions that regulate mood and motor functions in the central nervous system. A review of the literature suggests that changes similar to those observed in the behaviors of offspring exposed to vortioxetine in early life also occur as a result of prenatal exposure to the antiepileptic drug valproic acid (44, 45). Prenatal valproic acid exposure is a model used to induce experimental autism in rodents, and it is interesting to see behavioral changes in offspring after vortioxetine exposure similar to those in autistic animals. This similarity becomes even more interesting when one takes into account clinical studies suggesting an association between maternal antidepressant exposure and the development of autism spectrum disorder in children (16-19). As an antidepressant drug, modulating monoaminergic neurotransmission in brain, vortioxetine may also have such a potential. Both our preclinical results demonstrated in this study and previous findings of deleterious neurodevelopmental effects of early-life vortioxetine exposure on offspring (22) support this possibility. On the other hand, in order to be able to claim that prenatal and lactational vortioxetine exposure produces an autism-like behavioral profile in the offspring, the presence of social interaction deficits, which is one of the basic criterion of the autistic phenotype (46), needs to be demonstrated. Moreover, other behavioral patterns commonly seen in autism spectrum disorders such deficits in sensorimotor gating, altered sensitivity to sensory stimuli, altered eye blink conditioning and impaired reversal learning should also be investigated in further studies (44, 47).

This study has some limitations. First, healthy pregnant females were used for this study. However, if this study had been conducted on pregnant animals that were depressed using methods such as prenatal stress or restraint stress, it would have been possible to obtain data closer to the clinical conditions (48). Another limitation of this study is that behavioral studies were conducted only with male offspring. Although the reason for this choice was to avoid the confounding effect of hormonal fluctuations in female rats on the experimental data, it is clear that the effects of early-life vortioxetine exposure on female offspring should also be investigated. Additionally, further molecular studies are needed to elucidate the pathophysiological mechanisms underlying the behavioral changes induced by vortioxetine exposure in offspring and to better interpret the data obtained.

CONCLUSION

The preclinical findings obtained in this study indicated that maternal exposure to vortioxetine, especially at high

doses, may not be safe for the baby and suggested that this drug may not be superior to other antidepressants in terms of use in the prenatal and lactational periods. On the other hand, comprehensive clinical studies are needed on children of mothers who used this drug before birth and during breastfeeding to gain a clearer understanding of the short – and long-term effects of early-life vortioxetine exposure on children.

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Author Contributions:

Research idea: Ö.D.C., B.E.

Acquisition of data for the study: Ü.K., C.Y., M.E.

Analysis of data for the study: Ö.D.C., Ü.D.Ö.

Interpretation of data for the study: Ö.D.C., Ü.D.Ö., B.E.

Drafting the manuscript: Ö.D.C., Ü.D.Ö.

Revising it critically for important intellectual content: Ö.D.C., Ü.D.Ö., B.E.

Final approval of the version to be published: B.E., Ö.D.C., Ü.D.Ö., Ü.K., C.Y., M.E.

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