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Impact of Valproate and Levetiracetam Exposure on GAERS Behavior During Pregnancy

Melis Yavuz[1], Berk Can Kantarcı[2], Ahmet Şanlı[2], Şeyhmus Gavaş[2], Zehra Nur Turgan Aşık[3], Türkan Koyuncuoğlu[4], Özgür Kasımay[4], Filiz Onat[5]

[1]Acıbadem Mehmet Ali Aydınlar University Faculty of Pharmacy, Department of Pharmacology, İstanbul, Turkey

[2]Marmara University Faculty of Medicine, 6th Year Student, İstanbul, Turkey

[3]Marmara University Faculty of Medicine, Department of Medical Pharmacology, İstanbul, Turkey

[4]Marmara University Faculty of Medicine, Department of Medical Physiology, İstanbul, Turkey

[5]Acıbadem Mehmet Ali Aydınlar University Faculty of Pharmacy, Department of Pharmacology; Acıbadem Mehmet Ali Aydınlar University, Institute of Health Sciences, Department of Neurosciences, İstanbul, Turkey

Melis Yavuz MD

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Corresponding Author: Filiz Onat MD, E-mail: filiz.onat@acibadem.edu.tr

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Abstract

Objective: Valproate (VPA) and levetiracetam (LEV) are frequently prescribed for the management of idiopathic generalized seizures; however, their well-documented teratogenic effects raise concerns when administered to pregnant epileptic patients. This study aimed to assess the impact of VPA and LEV exposure during pregnancy on Genetic Absence Epilepsy Rats from Strasbourg (GAERS).

Methods: Female GAERS rats were categorized into three groups: saline-treated (n=6), VPA-treated (200 mg/kg, n=4), and LEV-treated (50 mg/kg, n=6). Intraperitoneal injections were initiated from mating start and continued until partition. Locomotor activity and anxiety-like behavior were evaluated using open-field and hole-board tests for the VPA-treated and VPA- and LEV-treated groups; respectively. These tests were conducted both before and during pregnancy.

Results: Across all groups, open-field testing demonstrated a tendency toward reduced locomotor activity parameters compared with pre-pregnancy, with VPA treatment showing significance ($p<0.05$). The hole-board test indicated a trend toward decreased rearing and hole exploration, coupled with increased freezing behavior in the saline- and VPA-treated groups. The LEV-treated group showed an elevation in freezing behavior and a decline in hole exploration.

Conclusion: Although minimal effects on anxiety-like behaviors were noted in anti-seizure drug-treated rats, subtle tendencies were evident in the hole-board test. VPA and LEV administration resulted in depressive parameters in the locomotor activity test. These findings emphasize the need for caution when prescribing and using VPA and the LEV during pregnancy in terms of maternal behavior and mood.

Keywords: GAERS, valproic acid, pregnancy, levetiracetam, maternal behavior

INTRODUCTION

Genetic Absence Epilepsy Rats from Strasbourg (GAERS) is a well-defined and validated animal model that has emerged as a valuable model for investigating the mechanisms underlying absence epilepsy.[1,2] With a genetic predisposition to absence seizures closely resembling those observed in humans, GAERS have provided researchers with a platform to decipher the intricate interplay between genetics, neural circuitry, and behavior, as well as sharing similar vital characteristics with human absence seizures and similar pharmacosensitivity to antiseizure drugs.[3]

Valproate (VPA) and levetiracetam (LEV), the two broad-spectrum antiseizure drugs with antiabsence effects and have high efficacy in managing seizures in epileptic patients,[4] although the effect of the latter has been discussed.[5] VPA is highly teratogenic, especially when administered during the first trimester of pregnancy, and is associated with significant congenital anomalies such as spina bifida, atrial septal defect, and cleft lip-palate. In addition, prenatal exposure to VPA has been linked to cognitive and developmental delays, and some studies suggest an increased risk of autism spectrum disorders in children.[6-11]

Compared with VPA, LEV has been considered to have a relatively safer profile in terms of teratogenic effect.[12-14] While some studies have suggested a slightly increased risk of certain congenital malformations, the overall risk appears to be lower than that associated with

VPA.[15] In particular, recent studies in humans have reported the LEV to be a safer alternative to VPA[16] or lamotrigine for teratogenicity.[17] However, data on the teratogenic effects of LEV are still evolving, and more research is needed to establish a clear understanding of its safety during pregnancy. Our team also showed congenital abnormalities in GAERS rats exposed to both VPA and the LEV in utero.[18] VPA and LEV have also shown ahigher risk of adverse psychobehavioral outcomes in the children of epileptic mothers, as well.[19]

Unlike offspring, there are only few studies addressing maternal behavior during pregnancy. Several studies have reported an increased risk of anxiety and depression in pregnant women taking VPA.[20] LEV might have a positive impact on anxiety-related behaviors measured by the elevated-plus maze test in a specific pathogen- free Sprague-Dawley rat model.[21] Other reports have shown individual anger-, aggression-, or depression-related behavioral outcomes with LEV monotherapy.[22] Recent reports in animals show that VPA induces cannibalistic behavior in mothers.[18,23] Conversely, another study showed that rats exposed to VPA during lactation exhibited extended pup nursing and increased active behaviors at specific postpartum days, whereas those exposed during pregnancy and lactation showed no significant impact on maternal care.[24]

In this study, we hypothesized that exposure to VPA and the LEV during pregnancy affects the behavior of pregnant rats. To investigate the potential impact of prenatal exposure to VPA/LEV on the behavior of pregnant GAERS, we injected pregnant GAERS with VPA or LEV and evaluated their locomotor and anxiety behaviors.

METHODS

Animals and Experimental Design

Female adult GAERS (n=22) were sourced from the breeding colony of the Department of Medical Pharmacology, Marmara University Faculty of Medicine. The animals were housed in a controlled environment at 21±3 °C with a 12-hour light/dark cycle (lights on at 8 am) and provided *ad libitum* access to food and water. Ethical clearance was obtained from the Marmara University Ethical Committee for Experimental Animals (protocol number: 108.2018.mar, date: 03.12.2018), in accordance with Directive 2010/63/EU of the European Parliament and Council.

GAERS were randomized into three groups: saline-treated (n=6), VPA-treated (n=8), and LEV-treated (n=8). Mating cages containing pairs of female rats from the same treatment group and a randomly selected male GAERS were established, with a total of three rats per cage. Twice-daily treatments of saline, VPA, and the LEV were initiated from the first day in the mating cage and continued until parturition.

MAIN POINTS

- This study provides evidence for the effect of levetiracetam (LEV) and valproate (VPA) on altered maternal behavior during pregnancy.
- Increase in freezing behavior and a decrease in hole exploration was observed in Genetic Absence Epilepsy Rats from Strasbourg (GAERS) treated with LEV.
- Locomotor activity parameters were decreased in pregnant GAERS treated with VPA.

Drug Injections

Seizure-controlling doses of VPA (200 mg/kg) and LEV (50 mg/kg) were determined to provide effective control of seizures and were selected based on established efficacy.[1,25] VPA (Depakin, 400 mg/4 mL) or LEV (Keppra, 500 mg/5 mL) were dissolved in 2 mL or diluted with 5 mL of saline (0.9% NaCl) for dose adjustment. Final solutions of saline, VPA (200 mg/mL), or LEV (50 mg/mL) were injected intraperitoneally at a volume of 1 mL/kg body weight according to their respective groups twice daily (at 10 am and 4 pm) to their respective groups, starting from the first day of placement in mating cages and continuing until parturition.

Open Field Test for Locomotor Activity

In these experiments, VPA (200 mg/kg, n=5) treated groups before and after PA injections (7th day) were used, and the experiments were performed at the same daytime slot (09:00-11:00 am). The animals were placed in a 40 × 40 × 40 cm seized open area test apparatus (Locomotor Activity Cage ACT 508, Commat, Ankara, Turkey) with an animal exposure of 150 lux light. The system was equipped with infrared photocells and integrated Activity Metering Software II version 2.1, in which the location of the test animal was recorded with an accuracy of 100 ms. The total distance and stereotypic activity of rats were evaluated. All parameters were calculated automatically by the program. The activities of grooming, chewing, gnawing, sniffing, orofacial movements, vibrissae twitching, and head weaving were classified as stereotypic activities.

Hole-Board Test

The hole-board test was performed on female GAERS treated with saline (n=6), VPA (200 mg/kg, n=4) and the third with LEV (50 mg/kg, n=6). The test was performed before the injections, during pregnancy, and post-term. The hole-board apparatus employed an enclosed wooden board measuring 40 × 40 × 40 cm, featuring 16 equally spaced cylindrical holes with a diameter of 3.8 cm. Each trial spanned a duration of 5 min, starting with the placement of the subject at the center of the board. A video camera positioned above the apparatus mounted on a tripod recorded the trials. Subsequently, two observers analyzed the 5-minute footage of each subject. Parameters, including head dipping frequency, rearing instances, and freezing time were quantified.

In this context, 'head dipping behavior' referred to instances where the animal inserted its head into a hole to a depth such that the subject's eyes were level with or below the hole-board apparatus floor. The term 'freezing time' denoted periods when no movement of the body or head was observed. Rearing was noted when the rat elevated itself onto its hind legs, with the forepaws either supported or unsupported by the walls. A decrease in head dipping frequency and rearing instances, coupled with an increase in freezing time, were interpreted as indicators of reduced exploratory behavior linked to heightened anxiety levels.[26,27]

Statistical Analysis

All statistical analyzes were performed using GraphPad Prism version 8.00 (GraphPad Software, San Diego, USA). Statistical analysis of locomotor activity in the VPA-treated groups before and after injections. Unpaired t-tests were used to analyze stereotypic, ambulatory, vertical, and horizontal activities. To compare

rearing, hole exploring, and increase in freezing behavior between female GAERS treated with saline (n=6), VPA (200 mg/kg, n=4) and with LEV (50 mg/kg, n=6, before the injections, during the pregnancy and post-term two-way ANOVA design with 2 factors "time" and "treatment" followed by the Tukey's test, was used. For the comparison of the three treatment groups, with 2 factors "treatment" (3 levels: saline, VPA and LEV) and "Injections" (3 levels: before injection, during pregnancy and post-term) were applied. The data are represented as t(df)=t-value, p=p-value for t-tests and "F(DFn, DFd)=F value, p value" for two-way ANOVA with $p<0.05$ significant difference.

RESULTS

Effect of Acute Injection of VPA on the Locomotor Activity Parameters of Pregnant GAERS

The stereotypic, ambulatory, vertical, and horizontal activity of GAERS before and after injections of VPA were compared for a duration of 5 min. There were significant differences in the stereotypic, vertical, and horizontal activity parameters. For the stereotypic activity t(10)=4.46, p=0.001 (Figure 1A), for the vertical activity t(10)=8.39, $p<0.0001$ (Figure 1C), and for the horizontal activity is t(10)=4.59, p=0.001 (Figure 1D). Although there were no significant differences for the ambulatory activity, the p value was 0.057 and t(10)=2.15 (Figure 1B).

There were also significant differences in the resting behavior and total distance taken by pregnant GAERS. For the resting behavior t(10)=2.4, p=0.03 (Figure 1E) and for the total distance; t(10)=3.07, p=0.01 (Figure 1F).

Effect of Acute Injection of VPA and the LEV on the Rearing Behavior, Head Dipping Frequency, and Freezing Behavior of Pregnant GAERS

The rearing behavior of female GAERS treated with saline (n=6), VPA (200 mg/kg, n=4) and with LEV (50 mg/kg, n=6), before the injections, during pregnancy, and post-term were evaluated. Significant variations in rearing behavior were observed in GAERS rats injected with GAERS during pregnancy, contrasting pre-injection levels [F(2, 16)=8.89, p=0.003, Figure 2A]. Analysis of freezing behavior revealed statistically significant differences attributed to treatment: F(2, 16)=7.3, p=0.006 during pregnancy and F(2, 16)=8.27, p=0.003 postpartum, specifically with LEV in comparison to the saline group (Figure 2B).

In terms of head dipping frequency, significant treatment effects were observed: F(2, 16)=9.3, p=0.002 during pregnancy and F(2, 16)=4.69, p=0.025 postpartum, both indicating that LEV-treated rats differed from the saline group (Figure 2C), according to two-way ANOVA.

The results from the hole-board test displayed a tendency toward reduced rearing and hole exploration, coupled with heightened freezing behavior in the saline and VPA-treated groups. Conversely, the LEV-treated group exhibited increased freezing behavior and diminished hole exploration.

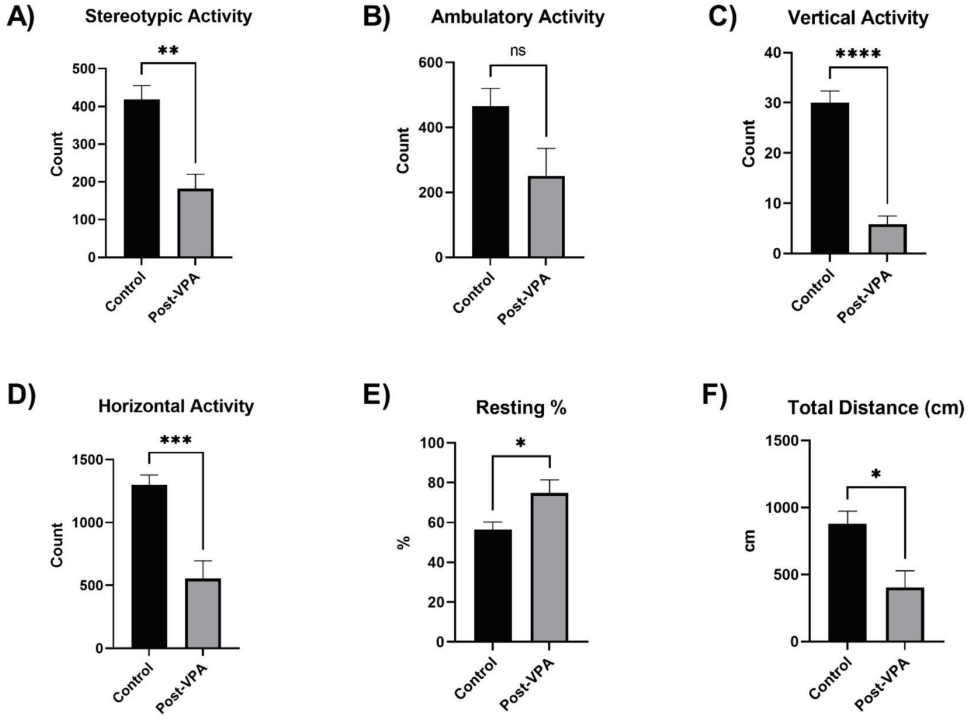

Figure 1. Comparison of locomotor activity parameters and behavioral traits in GAERS before and after VPA injections. The locomotor activity parameters of GAERS were evaluated before and after VPA injections. The figures present the distinct activity parameters and behavioral traits analyzed in this study. (A) Stereotypic activity was significantly altered following VPA injections; p=0.001, indicating changes in repetitive, non-goal-directed behaviors; (B) Ambulatory activity exhibited a trend toward modulation in response to VPA injections; (C) Vertical activity displayed a substantial decrease, indicating decreased vertical movements; (D) Horizontal activity was significantly decreased by VPA injections; (E) Resting behavior of pregnant GAERS exhibited a significant increase post-VPA injections; (F) Total distance traveled by pregnant GAERS also displayed a significant decrease following VPA injections. Error bars represent SEM
GAERS: Genetic Absence Epilepsy Rats from Strasbourg, VPA: Valproate, LEV: Levetiracetam, SEM: Standard errors of the mean

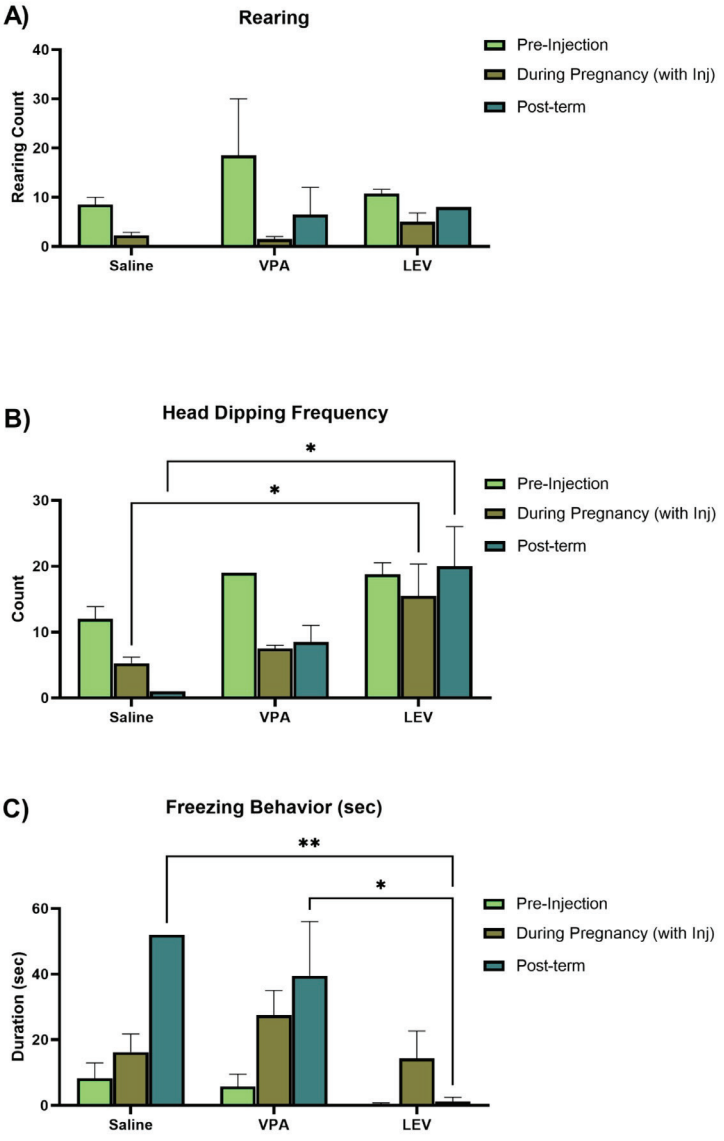

Figure 2. Effects of pharmacological treatments on maternal behavior and anxiety-related responses in female GAERS. Rearing behavior, freezing behavior, and head-dipping frequency of female GAERS were assessed following treatment with saline, VPA, and LEV during different phases of pregnancy and postpartum. Pregnant rats (n=6 per group) were administered saline, VPA (200 mg/kg), or LEV (50 mg/kg), while pre-injection pregnant rats served as controls (n=4 VPA, n=6 LEV). Behavioral variations were analyzed using two-way ANOVA. (A) Rearing behavior displayed significant differences among GAERS rats injected with treatments during pregnancy compared with pre-injection levels; (B) Freezing behavior exhibited treatment-specific effects during pregnancy and postpartum. LEV-treated rats showed increased freezing behavior in contrast to the saline group; (C) Head dipping frequency during pregnancy and postpartum revealed significant treatment effects. LEV-treated rats displayed distinct head dipping behavior compared with the saline group GAERS: Genetic Absence Epilepsy Rats from Strasbourg, VPA: Valproate, LEV: Levetiracetam, SEM: Standard errors of the mean

DISCUSSION

Our findings demonstrate: (1) decreased stereotypic, overall activity, and increased resting behavior of pregnant GAERS with chronic VPA treatment; (2) decreased rearing and hole exploration coupled with heightened freezing behavior in the saline and VPA-treated groups; (3) increased freezing behavior and diminished hole exploration in the LEV-treated group.

Behavioral assessments offer valuable methods for analyzing the potential effects of drugs and concurrent psychiatric irregularities. This is particularly significant in our investigation because of the relevance of the GAERS model as an accurate portrayal of human absence epilepsy, exhibiting documented social, behavioral, and psychiatric deviations.[28,29]

The findings of our study suggest differential effects of VPA and LEV on maternal behavior and anxiety-related responses in GAERS rats during pregnancy and postpartum periods, especially with the hole-board test. The results indicate anxiety-like behaviors and a general decrease in activity. Previously, we performed behavioral tests on male adult GAERS to analyze if any changes in arousal could be observed in the locomotor activity at baseline. Elevated stereotypic activity was observed in the GAERS group treated solely with a vehicle in contrast to the Wistar group, and the alpha antagonist drug also suppressed these stereotypic activities.[30] Stereotypic behavior, which is linked to excessive dopaminergic activity, is known to be mitigated by D1 receptor antagonism.[31] This mitigation of stereotypic activity could imply an indirect stabilization of the dopaminergic system.[32] VPA induces dopamine release in the amygdala without stimulation, dopamine release triggered by a conditioned stimulus, and dopamine release during methamphetamine sensitization.[33] In another study, VPA led to a rise in depressive symptoms and deterioration of dystonia in D2 supersensitivity.[34] Therefore, VPA may decrease the increased stereotypic behavior of the GAERS model. On the other hand, increased resting behavior and decreased activity may indicate depressive symptoms.[35]

LEV-induced psychiatric symptoms are reported as hypomanic symptoms,[36] aggression, depression,[22] and some of them are found to be irreversible.[37] On the other hand, recently, the LEV has been shown to have cognitive advantages,[38] with increased activity in the prefrontal cortex.

Study Limitations

As a limitation to our study, we only had the chance to observe throughout pregnancy, where physiological inactive states occur, and this will decrease the interpretation of locomotor activity data. Another limitation is that we could not perform locomotor activity tests on LEV-treated animals, and because many studies in the literature report dose-dependent teratogenicity,[39-41] and as a rule of thumb, dose-dependent influences on anxiety,[21] our study is limited due to the use of single doses

CONCLUSION

The available research suggests that both LEV and VPA may exhibit beneficial effects in mitigating abnormalities associated with dopaminergic excess. However, it is important to approach their usage cautiously, particularly in cases involving depressive states during pregnancy. The current body of literature concerning maternal mental health during pregnancy remains limited, warranting more comprehensive investigations into the potential behavioral and mood-related alterations resulting from the

administration of antiseizure drugs among pregnant women. Further studies in this domain are imperative to better understand the intricate interplay between medication use, dopaminergic modulation, and maternal mental well-being throughout pregnancy.

Ethics

Ethics Committee Approval: The study was approved by the Marmara University Ethical Committee for Experimental Animals (protocol number: 108.2018.mar, date: 03.12.2018).

Informed Consent: Animal experiment.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.O., Concept: M.Y., B.C.K., A.Ş., Ş.G., Z.N.T.A., F.O., Design: M.Y., B.C.K., A.Ş., Ş.G., Z.N.T.A., F.O., Data Collection or Processing: T.K., Ö.K., F.O., Analysis or Interpretation: F.O., Literature Search: F.O., Writing: M.Y., F.O.

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