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Research Article

Effects of sodium valproate on anxiety and depression in WAG/Rij rats with absence epilepsy

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ABSTRACT

Objective: Anxiety and depression are common comorbidities in patients with epilepsy. Sodium valproate is a long-established antiepileptic drug used for seizure control. The present study aimed to evaluate the effects of sodium valproate on anxiety-related behavior in genetically determined absence epileptic WAG/Rij rats using the open field test.

Materials and Methods: Twenty-eight WAG/Rij rats were randomly divided into four groups (n = 7/group): control, sodium valproate (VPA) 50 mg/kg, VPA 100 mg/kg, and VPA 200 mg/kg. Valproate was administered intraperitoneally once daily for 21 days. The control group received saline (0.5 ml/kg, i.p.). At the end of the treatment period, anxiety-related behavior was assessed using the open field test for 5 minutes under video recording. Horizontal locomotor activity, vertical activity (rearing), and grooming behavior were analyzed.

Results: Compared with the control group, low-dose VPA (50 mg/kg) significantly increased horizontal locomotor activity. Higher doses of VPA did not produce significant changes in locomotion. Grooming behavior increased in the VPA 100 and 200 mg/kg groups, while rearing behavior did not differ between groups.

Conclusion: Chronic VPA at 50 mg/kg increased horizontal activity in the open field, a pattern consistent with an anxiolytic-like profile in this assay. VPA at 100–200 mg/kg increased grooming, indicating a dose-dependent modulation of self-directed behavior; however, because grooming can reflect multiple behavioral states (e.g., stress-coping/displacement, arousal changes, or stereotypy), this finding should not be interpreted as a specific depression-related effect without additional behavioral and ethological analyses.

Keywords: sodium valproate, anxiety-like behavior, depression, absence epilepsy, WAG/Rij rats

Introduction

Epilepsy is a chronic neurological disorder frequently accompanied by psychiatric comorbidities, particularly anxiety and depression (1). Approximately one-third of patients with epilepsy experience clinically significant mood disorders, which are associated with poorer quality of life and reduced treatment response (2). However, standard antiseizure medications often fail to address these psychiatric symptoms (3) adequately.

The Wistar Albino Glaxo/Rijswijk (WAG/Rij) rat is a well-established genetic model of absence epilepsy that also exhibits depression-like behaviors, including reduced exploration and anhedonia (4,5). Suppression of spike–wave discharges has been shown to alleviate these behavioral comorbidities (6).

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Sodium valproate (valproic acid, VPA) is a broad-spectrum antiepileptic drug widely used for generalized epilepsies, including absence seizures, and also functions as a mood stabilizer. Its mechanisms involve enhancing GABAergic neurotransmission and modulating neuronal excitability (7). Preclinical studies demonstrate dose-dependent anxiolytic and antidepressant-like effects of VPA, with higher doses producing sedative actions comparable to benzodiazepines (7,8).

To the best of our knowledge, the effects of sodium valproate on anxiety-like behavior have not been previously investigated in WAG/Rij rats. At the same time, only one study has reported antidepressant-like outcomes following chronic treatment in this model. Accordingly, the present study provides the first integrated assessment of sodium valproate's effects on both anxiety- and depression-related behaviors in the WAG/Rij model of absence epilepsy.

In the present study, we aimed to evaluate the effects of chronic valproate treatment on anxiety- and depression-related behaviors in WAG/Rij rats, a model of absence epilepsy. We hypothesized that valproate treatment would modulate these behaviors in a dose-dependent manner – specifically, that a low dose of VPA might reduce anxiety-like behavior (manifested as increased exploratory activity in the open field). In contrast, higher doses might have sedative effects and potentially lessen depression-like signs (for example, by normalizing grooming or other stress behaviors). By comparing the open field metrics across control and VPA-treated groups, our goal was to determine whether chronic valproate can alleviate the anxiety and depression tendencies associated with genetic absence epilepsy in WAG/Rij rats.

Materials and Methods

Animals and experimental design

In the present study, 6-month-old WAG/Rij rats (250 ± 24) with genetic absence epilepsy were used. All animals were allowed to acclimatize to the laboratory environment for one week before the experiments. During this period, food and water were provided ad libitum. All experimental procedures were performed between 09:00 and 12:00 each day to maintain circadian rhythm consistency. Rats were housed in standard cages under controlled environmental conditions (22–25 °C, 12-h light/12-h dark cycle). Body weights were recorded at the beginning and at the end of the study. All procedures were approved by the Tokat Gaziosmanpasa University Animal Ethics Committee (Approval No: 51879863-15).

Experimental groups

Animals were randomly assigned to four groups as follows:

WAG/Rij Control group: saline (0.5 ml/kg, i.p.)

WAG/Rij + Sodium valproate: 50 mg/kg, i.p.

WAG/Rij + Sodium valproate: 100 mg/kg, i.p.

WAG/Rij + Sodium valproate: 200 mg/kg, i.p.

Drug

The VPA dose range (50, 100, and 200 mg/kg, i.p.) was selected to span low-to-high doses that have been evaluated in genetic absence epilepsy models and that cover reported anti-absence efficacy ranges in WAG/Rij rats. In a dose–response study in WAG/Rij rats, VPA doses up to 280 mg/kg (i.p.) were examined, and the ED50 for reducing spike–wave discharges was approximately 121 mg/kg. Therefore, 50 mg/kg was chosen as a low dose below the reported ED50, 100 mg/kg as an intermediate dose near the ED50, and 200 mg/kg as a higher dose within the effective range used in rodent studies.

Surgical procedure

All WAG/Rij rats with spontaneous absence epilepsy were subjected to electrocorticographic (ECoG) evaluation. Animals were fasted for 24 hours before surgery. Anesthesia was induced using ketamine (90 mg/kg) and xylazine (10 mg/kg). Following adequate anesthesia, the scalp was incised longitudinally (~3 cm), and the periosteum covering the skull was carefully removed. The bregma was identified as the reference point (Figure 1).

Using a microdrill with a 1-mm drill bit, three small burr holes were created in the skull. Tripolar electrodes were then implanted epidurally to allow ECoG recordings from the right frontal cortex, right occipital cortex, and left occipital cortex. Electrodes were positioned to contact the dura mater gently. Postoperative analgesia was provided by xylazine (10 mg/kg), administered immediately after surgery and subsequently at 8-hour intervals.

ECoG recording

Animals were allowed to recover for one week. Following recovery, a 3-hour baseline ECoG recording was obtained from each experimental group (Figure 1). After completion of baseline recordings, dexketoprofen or saline was administered to the respective groups, and ECoG activity was continuously recorded for an additional 3 hours. All recordings were performed using the MP150 Biopac System.

Electrocorticographic data were analyzed to determine the total number of spike-and-wave discharges (SWDs), SWD duration, number of spikes per burst, and mean amplitude values. Upon completion of ECoG recordings, animals underwent the open field test (Figure 1).

Open field test

The open field test was used to evaluate the baseline emotional state of the animals and to detect behavioral changes following experimental interventions. This test is widely employed to assess anxiety-related behavior, locomotor activity, and sedation.

All experimental groups received either saline (0.5 ml) or sodium valproate at the designated doses for 21 consecutive days. On day 21, rats were subjected to the open field test for a duration of 5 minutes. The open field test was conducted in a square arena (100 × 100 cm) divided into 64 equal squares. The arena walls were 25 cm high and constructed of white opaque material. Testing was performed in a quiet experimental room under constant

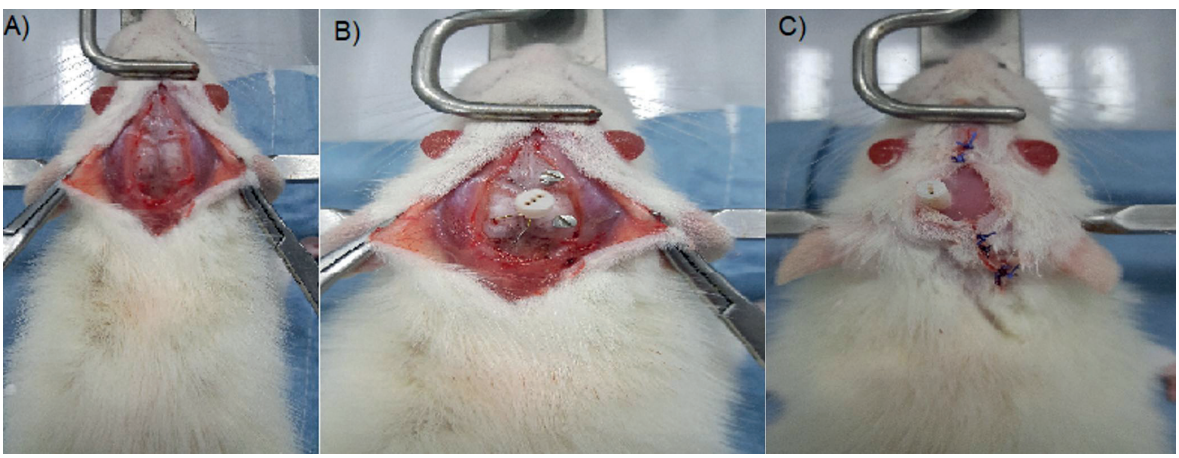


Figure 1. Surgical implantation of tripolar electrodes in anesthetized WAG/Rij rats.

(A) Exposure of the skull following scalp incision and creation of burr holes using a microdrill.

(B) Placement of the tripolar electrode onto the skull with contact to the dura mater.

(C) Fixation of the electrode to the skull using dental acrylic, followed by closure of the surgical incision with sutures.

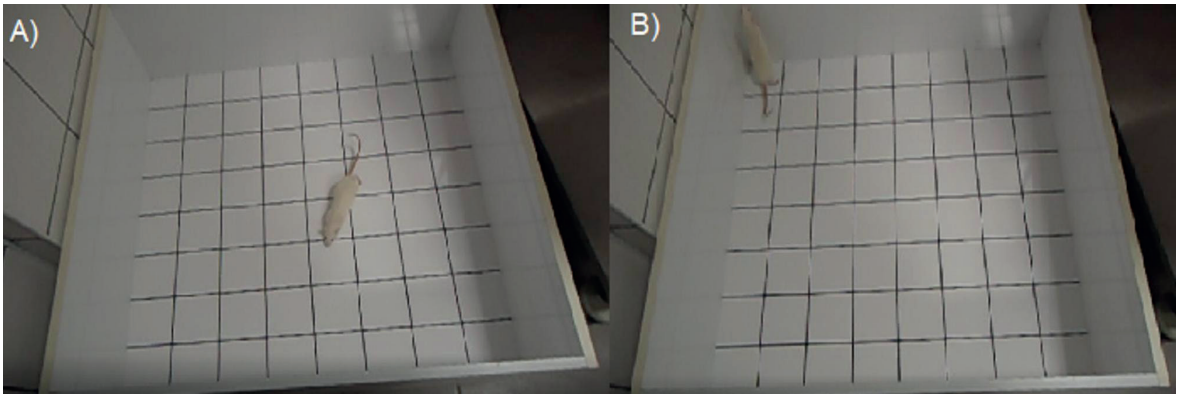


Figure 2. Open Field test.
A) Rat movements in the horizontal plane (transition from one square to another)
B) Rat movements in the vertical plane (rearing on the hind limbs)

illumination (150 lux measured at floor level in the center of the arena) and minimal external noise. Each rat was placed in the center of the arena and recorded for 5 min. After each trial, the arena was cleaned with 70% ethanol and allowed to dry to minimize olfactory cues (Figure 2).

Each animal was individually placed in the center of the arena, and behavior was recorded using a video camera for 5 minutes. During the test period, horizontal locomotor activity (number of squares crossed), vertical activity (rearing behavior), and grooming behavior were recorded and analyzed. Following data acquisition, the results were subjected to appropriate statistical analysis. Each rat was placed in the center of the arena and recorded for 5 min. After each trial, the arena was cleaned with [e.g., 70% ethanol] and allowed to dry to minimize olfactory cues.

Statistical analyses

Data are presented as mean ± SEM. Group differences were evaluated using one-way ANOVA, followed by Tukey's post hoc test for multiple comparisons. Exact p-values are reported for omnibus and post hoc tests where applicable. Effect sizes were reported as [η^2 or partial η^2] for ANOVA and Cohen's d for key pairwise comparisons. Statistical significance was set at $p < 0.05$. Analyses were performed using GraphPad Prism (version 7.0).

Results

ECOG recording

A dose-dependent decrease in both the number and duration of spike-and-wave discharges (SWDs) was observed (Figure 3).

Open field test

All behavioral data were analyzed using one-way ANOVA followed by Tukey's multiple comparisons test, with each group consisting of n = 7 animals.

Horizontal locomotor activity (number of squares crossed)

A one-way ANOVA revealed a statistically significant difference among groups ($F(3,24) = 11.99$, $p < 0.0001$, $R^2 = 0.5999$), indicating a strong treatment effect. Post hoc Tukey analysis showed that the VPA 50 mg/kg group exhibited a significant increase compared with the control group (mean difference = 27.86, 95% CI: 11.28–44.43, adjusted $p = 0.0006$), whereas no significant differences were observed between control and VPA 100 mg/kg ($p = 0.6966$) or VPA 200 mg/kg ($p = 0.7648$). Furthermore, locomotor activity in the VPA 50 mg/kg group

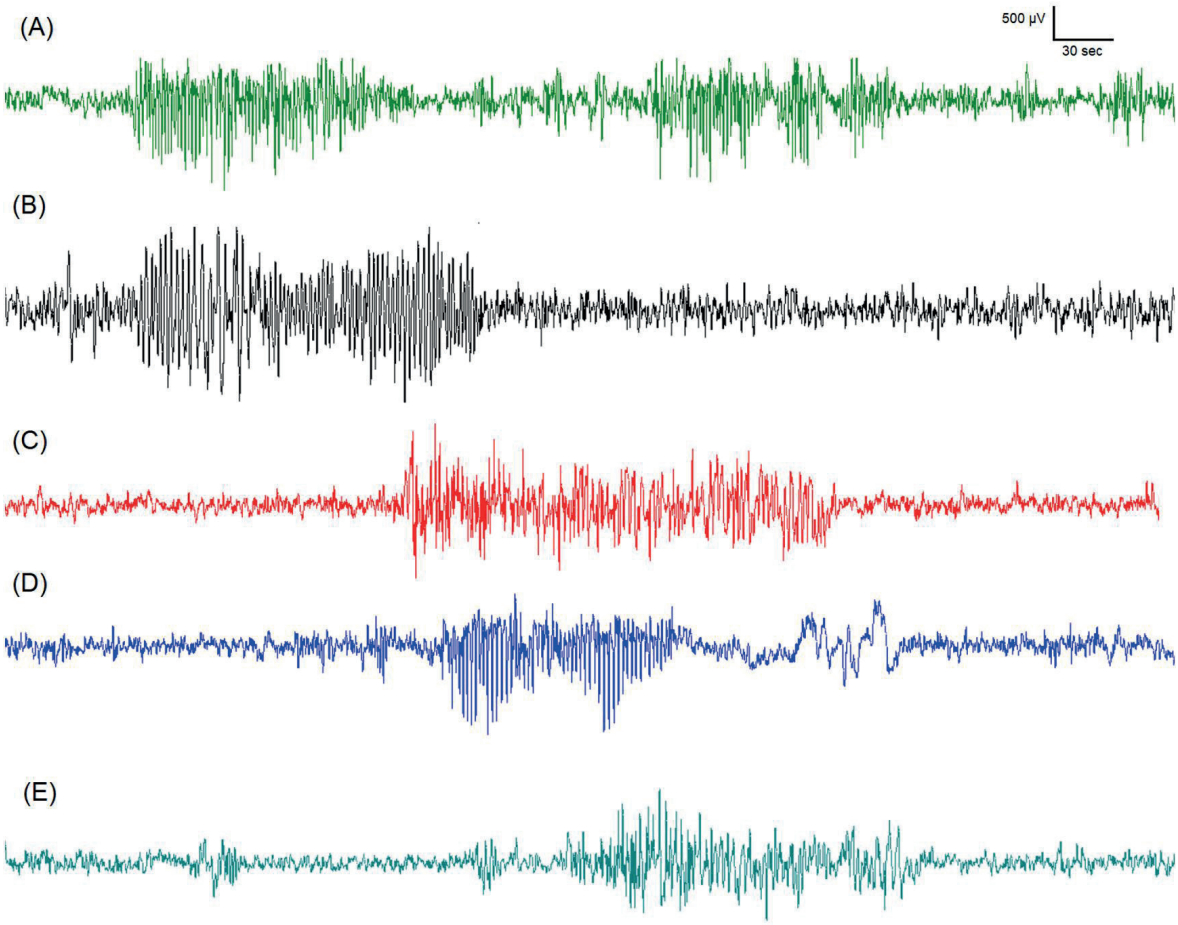


Figure 3. (A) Control group demonstrating baseline EEG activity. (B) VPA 50 mg/kg group showing increased frequency and amplitude of spike-and-wave discharges. (C) VPA 100 mg/kg group exhibiting moderate epileptiform activity. (D) VPA 200 mg/kg group showing reduced and more irregular discharges compared with lower doses. (E) [if applicable: treatment/other group] displaying attenuated epileptiform activity. Scale bars: 500 µV (vertical) and 30 s (horizontal).

was significantly higher than in both the VPA 100 mg/kg (mean difference = 21.29, p = 0.0084) and VPA 200 mg/kg groups (mean difference = 33.71, p < 0.0001), while no difference was detected between the VPA 100 mg/kg and VPA 200 mg/kg groups (p = 0.1920). The effect size was large ($\eta^2 \approx 0.60$) (Figure 4).

Grooming behavior

One-way ANOVA demonstrated a significant overall group effect ($F(3,24) = 18.45$, $p < 0.0001$, $R^2 = 0.6976$), indicating a very strong treatment effect. Post hoc analysis revealed that grooming activity was significantly increased in the VPA 100 mg/kg group (mean difference = -6.38, 95% CI: -11.18 to -1.58, p = 0.0062) and the VPA 200 mg/kg group (mean difference = -8.64, 95% CI: -13.44 to -3.84, p = 0.0002) compared with the control group, whereas no significant difference was observed between the control and VPA 50 mg/kg groups (p = 0.4501). In dose-dependent comparisons, grooming activity in the VPA 50 mg/kg group was significantly lower than that in both the VPA 100 mg/kg (p = 0.0001) and VPA 200 mg/kg groups (p < 0.0001), while no significant difference was found between the VPA 100 mg/kg and VPA 200 mg/kg groups (p = 0.5718). The effect size was very large ($\eta^2 \approx 0.70$) (Figure 5).

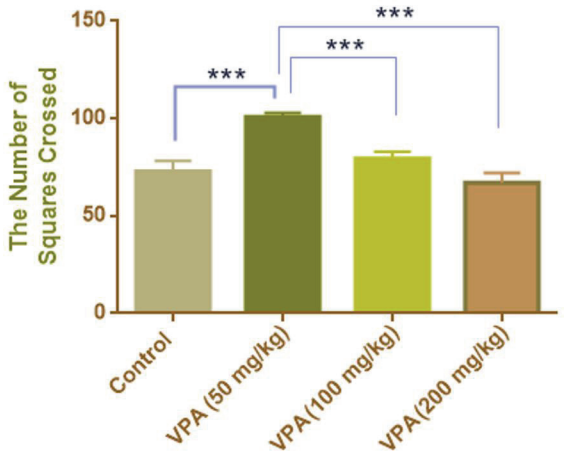


Figure 4. Horizontal locomotor activity of all experimental groups in the open field test. Horizontal movement was significantly increased in the low-dose sodium valproate group (VPA, 50 mg/kg) compared with the control group ($p < 0.05$). No significant differences were observed in the VPA 100 mg/kg or VPA 200 mg/kg groups relative to controls ($p > 0.05$). In addition, horizontal locomotor activity in the VPA 50 mg/kg group was significantly higher than that in the VPA 100 mg/kg and VPA 200 mg/kg groups ($p < 0.05$).

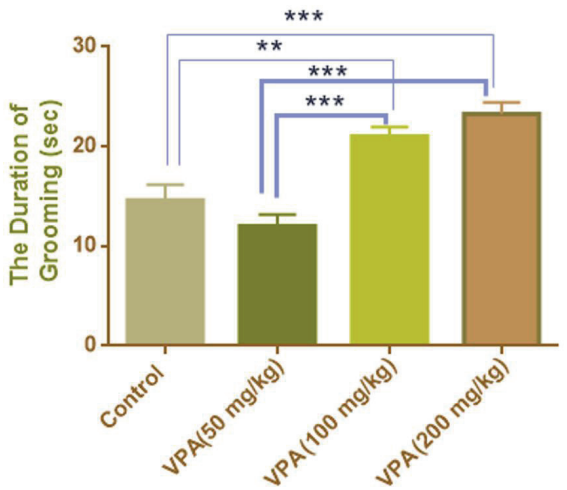


Figure 5. Grooming activity duration of all experimental groups in the open field test. Grooming behavior was significantly increased in the VPA 100 mg/kg and VPA 200 mg/kg groups compared with the control group ($p < 0.05$). No significant difference in grooming activity was observed in the low-dose sodium valproate group (VPA, 50 mg/kg) relative to controls ($p > 0.05$). In addition, grooming activity in the VPA 50 mg/kg group was significantly lower than that observed in the VPA 100 mg/kg and VPA 200 mg/kg groups ($p < 0.05$).

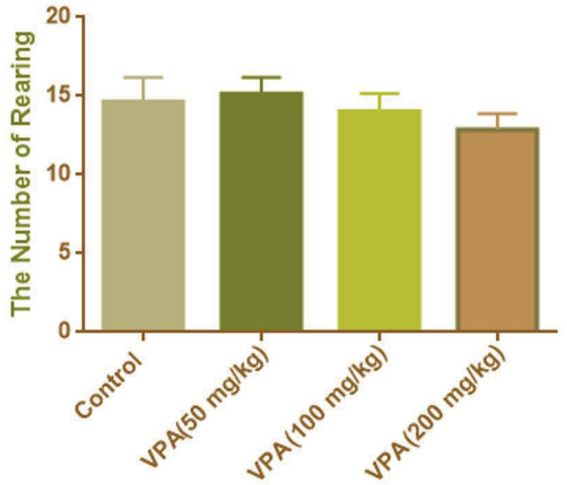


Figure 6. Vertical locomotor activity (rearing behavior) in the open field test. The number of rearing events did not differ significantly among the experimental groups or when compared with the control group ($p > 0.05$).

Vertical locomotor activity (rearing)

No statistically significant differences were observed among the groups. One-way ANOVA indicated no group effect ($F(3,24) = 0.65$, $p = 0.5907$, $R^2 = 0.075$), and all pairwise comparisons were non-significant (all adjusted $p > 0.55$). The corresponding effect size was small ($\eta^2 \approx 0.075$), suggesting a negligible treatment effect on vertical locomotor activity (Figure 6).

Discussion

To the best of our knowledge, this is the first study to investigate the effects of sodium valproate on both anxiety- and depression-like behaviors in the WAG/Rij model of absence epilepsy. Numerous in vivo and in vitro studies have been conducted to elucidate the molecular mechanisms underlying seizure activity in experimental epilepsy models using various pharmacological agents (9-11). Absence epilepsy represents a typical form of idiopathic generalized epilepsy and is most commonly observed during childhood. It is characterized by sudden, brief episodes of impaired consciousness, accompanied by bilateral,

synchronous, and symmetrical spike-and-wave discharges on electroencephalography (EEG), typically at 2.5–3.5 Hz and with amplitudes of 100–1200 μV.

In the present study, WAG/Rij rats were selected as a model of absence epilepsy. This strain was developed through inbred breeding of Wistar albino rats that spontaneously exhibit spike-and-wave discharge (SWD) activity. As a genetic animal model of absence epilepsy, WAG/Rij rats display clinical, pharmacological, and electrophysiological features that closely resemble those observed in human absence epilepsy (12). In addition to epileptic activity, the WAG/Rij model is characterized by depression-like comorbidities associated with absence epileptogenesis. In patients with epilepsy, anxiety and depression occur more frequently than in the general population. Therefore, the WAG/Rij rat model provides a suitable experimental platform for investigating anxiety- and depression-related behaviors accompanying absence seizures.

Previous studies have demonstrated that pharmacological suppression of absence seizures reduces both anxiety- and depression-like behaviors in epileptic rats (6). One of the limited studies investigating the effects of sodium valproate in the WAG/Rij model reported that chronic valproate treatment suppressed the development of absence seizures and significantly attenuated accompanying depression-like behaviors (13). In contrast, other genetic absence epilepsy models, such as GAERS, exhibit pronounced anxiety and anhedonia even before seizure onset, indicating apparent model-specific behavioral differences (14). In a GAERS-based study, sodium valproate was shown to exert sedative effects without exacerbating anxiety-like behavior (15). Findings from acquired epilepsy models are more heterogeneous; in the PTZ-kindling model, valproate effectively suppressed seizures but failed to reverse depression-like behavior when administered alone (16). Similarly, in the hippocampal kindling model, low-dose valproate combined with low-frequency electrical stimulation significantly reduced both anxiety- and depression-like behaviors (17).

The open field test is widely used to assess anxiety-like behaviors in rodents. In the present study, locomotor activity (horizontal movement; number of squares crossed), exploratory behavior (vertical activity; rearing), and grooming responses were evaluated in rats treated with sodium valproate (VPA). A reduction in locomotor activity is generally interpreted as an increase in anxiety-like behavior (18,19). Decreased exploratory behavior may reflect impaired novelty-seeking motivation, reduced interest in new environments, and features associated with anxiety and depressive disorders. Similarly, reduced grooming responses are considered to mimic social withdrawal, loss of interest, and anhedonia, which are core features of depression (20-24).

Self-grooming is an ethologically organized, self-directed behavior that can reflect multiple neurobehavioral states rather than a single affective construct. Depending on context, grooming may increase after novelty or mild stress as a displacement/coping response and may also present as repetitive or stereotyped behavior in some pharmacological or neuropsychiatric models (25-27). Moreover, stress-related grooming has been proposed to contribute to post-stress de-arousal and behavioral homeostasis (28). Accordingly, the increased grooming observed after VPA 100–200 mg/kg in the open field should be interpreted cautiously and may reflect altered stress responsivity, arousal, or repetitive behavioral expression rather than a specific depression-like phenotype. Because we quantified total grooming duration only (without microstructural pattern analysis such as bout number, bout duration, or grooming sequence structure), we cannot distinguish between displacement grooming and other grooming phenotypes. Future studies should incorporate ethological grooming microstructure and additional assays of depression- and anxiety-

related behavior to better triangulate affective state.

Valproate's anti-absence efficacy in WAG/Rij rats has been characterized previously in dose–response designs, with doses up to ~280 mg/kg (i.p.) and an estimated ED50 around 121 mg/kg for reducing spike–wave discharges (29). Functional tolerance to valproate's anti-absence effects at high exposure levels has also been reported in this model (30). More recently, chronic paradigms including valproate have been used to examine comorbidity-relevant outcomes and disease modification in WAG/Rij rats (13), and long-term oral VPA regimens (e.g., 300 mg/kg) have been implemented in WAG/Rij studies targeting epilepsy-related comorbid phenotypes (31). Our findings extend this literature by describing dose-dependent open-field behavioral changes after a 21-day VPA regimen.

Limitation

Relating rodent mg/kg dosing to human therapeutic exposure is inherently limited by species differences in absorption, distribution, metabolism, and sampling time relative to dosing. In clinical practice, typical total valproate therapeutic plasma concentrations are approximately 50–100 μg/mL for epilepsy (32). In rodents, higher peak plasma concentrations can occur shortly after i.p. dosing; for example, 200 mg/kg (i.p.) produced mean plasma levels of ~376 μg/mL at 30 min in a rat kindling study (33), while chronic dosing studies demonstrate pronounced peak–trough fluctuations over time (34). Plasma valproate levels were not measured in the present study, which limits direct comparison to therapeutic ranges; future work should include pharmacokinetic confirmation to strengthen translational interpretation.

Considering the behavioral outcomes observed in genetically absence epileptic WAG/Rij rats, our findings suggest that low-dose VPA reduces anxiety-like behaviors by enhancing locomotor activity, whereas higher doses may preferentially attenuate depression-like behaviors, as reflected by alterations in grooming activity.

Ethical approval

All procedures were approved by the Tokat Gaziosmanpasa University Animal Ethics Committee (Approval No: 51879863-15).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: HA; data collection: HA, OS; analysis and interpretation of results: HA, OS; draft manuscript preparation: HA. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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