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The Effect of Dapagliflozin on Absence Epilepsy in WAG/Rij Rats

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Abstract

Objective: Epilepsy is the most common chronic brain disease that affects millions of people worldwide. In the present study, we investigated the effects of dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, which has been recently introduced as a new drug for diabetes mellitus, on seizure activity in Wistar Albino Glaxo from Rijswijk (WAG/Rij) rats with genetic absence epilepsy.

Methods: Twenty-eight adult male WAG/Rij rats were divided into the following groups: Group 1, control; Group 2, dapagliflozin (1 mg/kg); Group 3, dapagliflozin (5 mg/kg); Group 4, dapagliflozin (25 mg/kg). The tripolar electrodes were placed while the patient was under general anesthesia. After a recovery period, three hours of basal electrocorticography (ECoG) recording was taken. Following the basal ECoG recording, dapagliflozin at doses of 1, 5, and 25 mg/kg was injected intraperitoneally. After the dapagliflozin injections, researchers recorded ECoG for another three hours. In the recordings, the total number and duration of spike-and-wave discharges (SWDs), and average SWD amplitudes were used to evaluate seizures.

Results: Compared to the control group, the administration of 1 mg dapagliflozin significantly decreased the number and duration of SWDs. Both parameters of SWD increased significantly in the 25 mg dapagliflozin group. The number and duration of SWDs did not change significantly between 5 mg dapagliflozin and the control groups. There were no significant changes in the average SWD amplitude values of all groups.

Conclusion: The results of the present study provided electrophysiological evidence regarding the role of SGLT2 inhibitors in the modulation of genetic absence epilepsy seizures.

Keywords: Absence epilepsy, dapagliflozin SGLT2, SWD, WAG/Rij

INTRODUCTION

Absence epilepsy, a subtype of idiopathic generalized epilepsy, accounts for 10-15% of pediatric cases and, despite its benign reputation, can persist into adulthood with associated cognitive deficits.[1,2] First-line treatments such as ethosuximide, valproic acid, and lamotrigine are effective in many cases, but drug resistance and adverse effects remain challenges.[3] This underscores the need for alternative therapies that also address underlying epileptogenic mechanisms.

The brain relies heavily on glucose metabolism for neuronal function, consuming nearly 20% of the body's total glucose.[4] Glucose uptake is mediated by facilitated glucose transporters (GLUTs) and sodium-glucose cotransporters (SGLTs).[5-7] Although SGLTs were initially identified in peripheral organs, recent findings confirm their presence in brain regions such as the hippocampus, cortex, and hypothalamus.[8] While SGLT2 is minimally expressed in the healthy brain tissue, it may be upregulated under pathological conditions, including epilepsy.[9]

Inhibition of SGLTs can limit intracellular glucose availability, potentially triggering energy imbalance and increased seizure susceptibility. Conversely, selective SGLT2 inhibition has shown neuroprotective effects in some models, possibly via enhanced ketogenesis, redox stabilization, and anti-inflammatory pathways.[10-12] Dapagliflozin, a selective SGLT2 inhibitor used for type 2 diabetes, has demonstrated both pro- and anti-epileptic effects in preclinical models. For example, phlorizin worsened seizures in the pilocarpine model,[13] while dapagliflozin reduced seizure activity and neuroinflammation in pentylenetetrazol (PTZ) and pilocarpine models.[9,14]

Wistar Albino Glaxo from Rijswijk (WAG/Rij) rats are a well-established genetic model of absence epilepsy, developing spontaneous spike-and-wave discharges (SWDs) akin to human absence seizures after three months of age.[15,16] This model provides a robust platform for evaluating anti-epileptic interventions targeting idiopathic generalized epilepsy.

In this study, we evaluated the acute, dose-dependent effects of dapagliflozin on absence seizures in WAG/Rij rats using in vivo electrocorticography (ECoG) recordings. To our knowledge, this is the first report examining SGLT2 inhibition in this genetic model, aiming to clarify the dualistic impact of dapagliflozin on seizure modulation and to explore SGLT2 as a metabolic target in epilepsy.

METHODS

Animals

In this study approved by Gaziantep University Animal Experiments Local Ethics Committee (approval no: 2019 HADYEK-57, date: 22.02.2020), 28 male WAG/Rij rats weighing 270±10 g were used for the experiments. Rats were housed in a fixed-temperature room (23±4 ºC) in a 12-hour light/12-hour dark cycle (the light turned on at 7 a.m. and turned off at 7 p.m.) with free access to food and drink. The following experimental groups were created with random assignment of seven rats in each group:

1. Control group (saline 2 mL/kg, intraperitoneal)

2. Dapagliflozin (1 mg/kg, intraperitoneal, 0.5 mL)

3. Dapagliflozin (5 mg/kg, intraperitoneal, 0.5 mL)

4. Dapagliflozin (25 mg/kg, intraperitoneal, 0.5 mL)

Drug

Dapagliflozin (≥98% purity, high-performance liquid chromatography, purified grade) was purchased from Sigma-Aldrich (Merck Germany, catalog no: SML2804) and freshly dissolved in sterile 0.9% saline for intraperitoneal administration, in accordance with previously published protocols using purified research-grade dapagliflozin in rodent epilepsy models.[14,17]

The doses of dapagliflozin (1, 5, and 25 mg/kg) were selected based on previous studies investigating the neuroprotective and anti-epileptic effects of SGLT2 inhibitors in rodent models,[9,14,17] as well as standard preclinical protocols for assessing dose-dependent responses. Dapagliflozin (intraperitoneal) was administered once, immediately following the completion of baseline ECoG recordings, to evaluate its acute effects on absence seizure activity. Intraperitoneal injection was chosen as the administration route because it ensures consistent systemic drug delivery and is widely used in experimental epilepsy models. Dapagliflozin exhibits partial blood-brain barrier (BBB) permeability under physiological conditions, achieving brain/plasma ratios of approximately 30-50%.[18]

Surgical Procedures

WAG/Rij rats were anesthetized with ketamine (90 mg/kg, intraperitoneal) and xylazine (10 mg/kg, intraperitoneal). With the help of a stereotaxic instrument, tripolar ECoG recording electrodes (Plastic Products Company, 333/2A) were placed in rats under anesthesia in accordance with the Paxinos and Watson atlas. "For ECoG recording, electrodes were placed at the following coordinates: anteroposterior (AP) +2.0, lateral (L) +3.5 (frontal region); AP -6.0, L +4.0 (parieto-occipital region); and a reference electrode on the cerebellum. After placement, the electrodes were fixed to the skull using cold dental acrylic. Following the stereotaxic surgery, the animals were kept in individual cages and allowed a week to recover.[15,19]

MAIN POINTS

- Low-dose dapagliflozin (1 mg/kg) significantly reduced the number and duration of spike-and-wave discharges (SWDs) in Wistar Albino Glaxo from Rijswijk rats.
- High-dose dapagliflozin (25 mg/kg) markedly increased both the number and duration of SWDs, suggesting a pro-epileptic effect.
- Mid-dose dapagliflozin (5 mg/kg) had no significant effect on seizure parameters.
- SWD amplitude remained unchanged across all treatment groups.
- The findings demonstrate that dapagliflozin has dose-dependent, bidirectional effects on absence seizure activity, highlighting its potential and risk in epilepsy treatment.

ECoG Recording and Drug Administration

After placing tripod electrodes for ECoG recording, the rats were allowed to recover for a week. After the recovery period, ECoG recordings were made in WAG/Rij rats, which moved freely in a noise-isolated room. First, the animals were accustomed to a recording cage (50×50×50 cm). After stereotaxic implantation of electrodes and a 7-day postsurgical recovery period, baseline ECoG recordings were performed for 180 minutes during the lights-on period (09:00 to 12:00) to minimize circadian rhythm effects. After completion of the baseline recording, the animals were allowed to rest for 24 hours without intervention. On the following day, between 9:00 and 12:00, dapagliflozin (1 mg/kg, 5 mg/kg, or 25 mg/kg) or sterile saline (control group) was administered intraperitoneally. Immediately after injection, a second EcoG recording session was initiated and continued for another 180 minutes. This procedure was applied consistently to all rats across the experimental groups (Figure 1).

Evaluation of ECoG Records

ECoG signals were recorded online using the PowerLab 16/35 data acquisition system (ADInstruments, Australia). In WAG/Rij rats, ECoG recordings were analyzed both before and after the administration of dapagliflozin, in the treatment groups and physiological saline in the control group. The primary parameters assessed were the number, duration, and amplitude of spontaneously occurring SWDs.

SWDs were identified based on their characteristic morphology: sharp, asymmetric, large-amplitude spikes followed by slow waves, in accordance with previously established criteria. Data were analyzed using LabChart v7.3.7 software (ADInstruments, Australia), which enables quantification of the frequency and amplitude of epileptiform discharges.

In the data analysis menu, the "spike shape" feature was used to set detection thresholds, allowing the software to differentiate SWDs from baseline cortical activity. Each automatically identified event was visually inspected to ensure it exhibited the hallmark SWD morphology. The total number and duration of SWD clusters, as well as the average spike amplitude (peak-to-peak), were calculated automatically.

Percent changes were calculated relative to the three-hour baseline recordings obtained prior to drug or saline administration. For each parameter (number, duration, and amplitude of SWDs), the percentage change was computed using the formula:

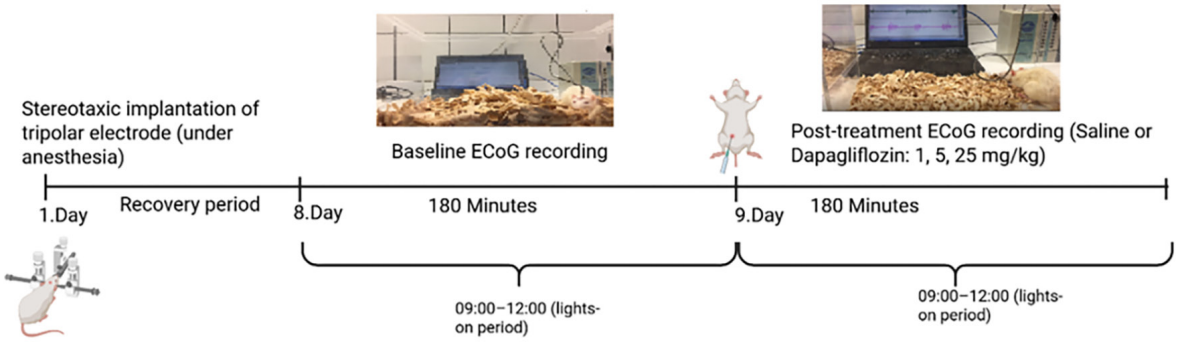

Figure 1. Experimental timeline of the study. Baseline and post-treatment ECoG recordings were performed in WAG/Rij rats following stereotaxic implantation of tripolar electrodes. Recordings were conducted during the lights-on period (09:00-12:00) on days 8 and 9. Dapagliflozin was administered intraperitoneally (1, 5, or 25 mg/kg) immediately before the second recording session
ECoG: Electrocorticography, WAG/Rij: Wistar Albino Glaxo from Rijswijk

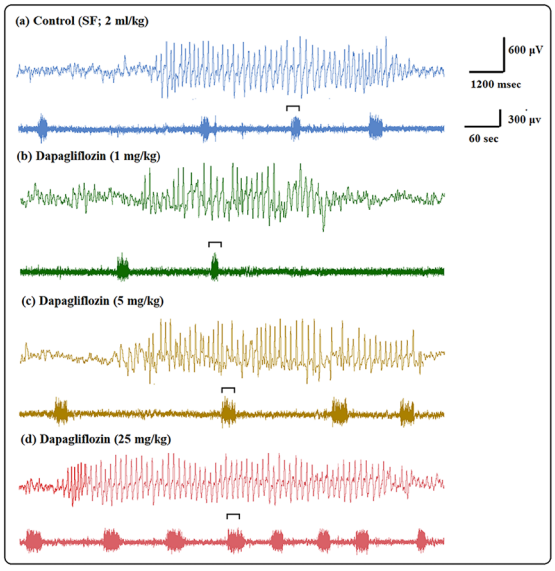

Figure 2. (a) control, **(b)** dapagliflozin (1 mg/kg), **(c)** dapagliflozin (5 mg/kg) and dapagliflozin (25 mg/kg) groups. Some representative ECoG recordings between 80th and 90th minutes (bar 300 millivolt (mV), 60 seconds (sec); bar 600 microvolts (µV), 1200 milliseconds (msec)
ECoG: Electrocorticography

Statistical Analysis

Parameters of baseline SWDs were calculated for each rat, including total number of SWDs, cumulative SWDs duration (seconds), and mean amplitude (µV). Following treatment, the same parameters were re-evaluated during the post-treatment ECoG recording. To control for inter-subject variability, each rat's post-treatment values were expressed as a percentage of its own baseline value. This normalization allowed for accurate group-level comparisons of treatment effects.

The data were analyzed statistically using SPSS 20.0 (IBM Corp., Armonk, NY, USA). First, the Kolmogorov-Smirnov test was applied to determine whether the data had a normal distribution. In the analysis of normally distributed data, the statistical difference among the groups was determined using one-way ANOVA followed by Tukey's post-hoc test. For the post-hoc test, $p<0.05$ was considered significant. GraphPad Prism version 7.0 (GraphPad Software, San Diego, CA, USA) was used for the graphics in statistical evaluations.

RESULTS

The Total Number of SWDs

In the baseline ECoG recordings, no significant differences in the total number of SWDs were detected among the groups (63.57±5.39, 65.14±6.99, 61.84±2.31, and 60.29±3.62 for the control, dapagliflozin 1 mg/kg, 5 mg/kg, and 25 mg/kg groups, respectively; $p>0.05$; Figures 2 and 3).

The total number of SWDs significantly decreased in the dapagliflozin 1 mg/kg group (35.71±2.45) compared to the control group (66.40±7.05) ($p<0.01$). No significant difference was observed between the dapagliflozin 5 mg/kg group (76.17±5.55) and the control group ($p>0.05$). However, the total number of SWDs was significantly higher in the dapagliflozin 25 mg/kg group (134.1±7.19) compared to the control group ($p<0.001$), the 1 mg/kg group ($p<0.001$), and the 5 mg/kg group ($p<0.001$) (Figures 1 and 2).

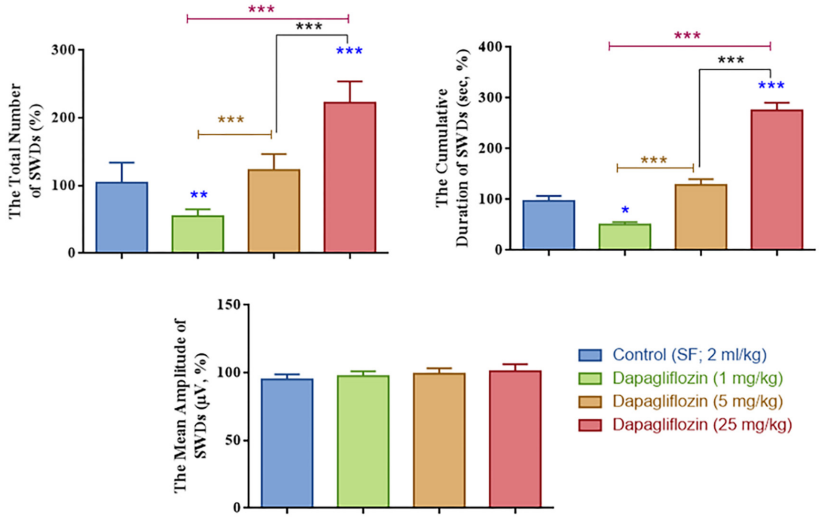

Figure 3. Effects of 1, 5, and 25 mg/kg dapagliflozin administration on **(a)** the total number, **(b)** the cumulative duration, and **(c)** the mean amplitude of SWDs in WAG/Rij rats with genetic absence epilepsy. SWD parameters were calculated from 180-minute ECoG recordings following treatment and normalized to each rat's own baseline values. Data are presented as percentage change (%), expressed as mean±SEM. Administration of 1 mg/kg dapagliflozin significantly reduced the total number and cumulative duration of SWDs compared to the control group (*p<0.05; **p<0.01). The 5 mg/kg dose showed no significant effect on SWD number, duration, or amplitude relative to controls (p>0.05). In contrast, 25 mg/kg dapagliflozin significantly increased both total SWD number and cumulative duration compared to the control, 1 mg/kg, and 5 mg/kg groups (***p<0.001). There were no significant differences in the mean amplitude of SWDs among the groups (p>0.05)
SWDs: Spike-and-wave discharges, WAG/Rij: Wistar Albino Glaxo from Rijswijk, ECoG: Electrocorticography, SEM: Standard error of the mean

The total number of SWDs was measured numerically, normalized to baseline values, and presented as a percentage in Figures 2 and 3.

The Cumulative Duration of SWDs

In the baseline ECoG recordings, no significant differences in the cumulative duration of SWDs were detected among the groups (442.3±16.89, 448.4±37.88, 418.1±24.65, and 405.7±27.95 seconds for the control, dapagliflozin 1 mg/kg, 5 mg/kg, and 25 mg/kg groups, respectively; p>0.05) (Figures 2 and 3).

The cumulative duration of SWDs was significantly reduced in the dapagliflozin 1 mg/kg group (227.4±22.27 seconds) compared to the control group (430.2±43.42 seconds) (p<0.05). The dapagliflozin 5 mg/kg group (538.5±48.09 seconds) showed no significant reduction compared to the control group (p>0.05). Conversely, the dapagliflozin 25 mg/kg group (1,117±62.04 seconds) exhibited a significant increase in cumulative SWD duration compared to the control group (p<0.001), the 1 mg/kg group (p<0.001), and the 5 mg/kg group (p<0.001) (Figures 2 and 3).

The cumulative duration of SWDs was measured numerically, normalized to baseline values, and presented as a percentage in Figures 2 and 3.

The Mean Amplitude of SWDs

In the baseline ECoG recordings, no statistically significant differences were observed in the mean amplitude of SWDs among the groups (control: 661.8±13.20 µV; dapagliflozin 1 mg/kg: 634.8±31.29 µV; 5 mg/kg: 646.7±31.28 µV; 25 mg/kg: 647.6±24.52 µV; p>0.05). Following treatment, the mean SWD amplitudes remained statistically unchanged between the control group (629.0±25.02 µV) and the dapagliflozin-treated groups (1 mg/kg: 619.2±23.28 µV; 5 mg/kg: 642.6±25.67 µV; 25 mg/kg: 654.4±34.53 µV; p>0.05). Amplitude measurements were obtained by averaging the peak-to-peak voltages of individual SWD events over the 180-minute recording period. Values were normalized to each subject's baseline amplitude and expressed as percentage change in Figures 2, 3; Tables 1,2.

DISCUSSION

In the present study, the low dose of dapagliflozin (1 mg/kg) suppressed absence seizures, while the high dose (25 mg/kg) showed an enhancing effect on absence seizures. A moderate dose of 5 mg/kg on the other hand, was found to have no effect on absence seizures.

Changes in neuronal energy metabolism are known to cause epileptic seizures.[20] GLUT type 1 deficiency syndrome was first described in 1991 in children with developmental retardation and infancy seizures.[21,22] Generalized SWDs have been observed in electroencephalography recordings of affected individuals, particularly during fasting states.[23] Glucose analogue ^{18}F-florodeoksiglukoz (^{18}F-FDG), is an indirect marker of neuronal activity and allows absolute measurement of cerebral glucose metabolism.[24] In studies with ^{18}F-FDG-positron emission tomography, it was shown that FDG absorption in epileptic foci increased during ictal activity, that is, during seizures, and decreased during the interictal period.[24] Experimental models have also demonstrated increased glucose utilization in epileptic foci.[25,26] Inhibition of SGLT causes lower glucose entry into the cell and, as a result, lower adenosine triphosphate (ATP) production. ATP is the energy source for performing various cell functions, including the operation of sodium-potassium and chloride pumps, and the preservation of resting membrane potential.[27] Therefore, SGLTs may be necessary for the survival of neurons under low glucose concentrations or anoxia.[8]

Table 1. SWD parameters recorded from baseline ECoG before SF and dapagliflozin injections

Groups	The total number of SWDs	The cumulative duration of SWDs (sec)	The mean amplitude of SWDs (μV)
Control (SF; 2 mL/kg)	63.57±5.38	442.3±16.89	661.8±13.20
Dapagliflozin (1 mg/kg)	65.14±6.99	448.4±37.88	634.8±31.29
Dapagliflozin (5 mg/kg)	61.84±2.30	418.1±24.65	646.7±31.28
Dapagliflozin (25 mg/kg)	60.29±3.62	405.7±27.95	647.6±24.52

Data are presented as mean±standard error of the mean.
ECoG: Electrocorticography, SWDs: Spike-and-wave discharges, SF: Saline formulation

Table 2. SWD parameters recorded from ECoG after SF and dapagliflozin injections

Groups	The total number of SWDs	The cumulative duration of SWDs (sec)	The mean amplitude of SWDs (μV)
Control (SF; 2 mL/kg)	66.40±7.04	430.2±43.42	629±25.02
Dapagliflozin (1 mg/kg)	35.71±2.44, [b]	227.4±22.27, [a]	619.2±23.28
Dapagliflozin (5 mg/kg)	76.17±5.55, [d]	538.5±48.09, [d]	642.6±25.67
Dapagliflozin (25 mg/kg)	134.1±7.18, [c,d,e]	1117±62.04, [c,d,e]	654.4±34.53

Data are presented as mean±standard error of the mean. $p<0.05$, $p<0.01$, $p<0.001$ compared to the control group; $p<0.001$ compared to the dapagliflozin 1 mg/kg group; $p<0.001$ compared to the dapagliflozin 5 mg/kg group.
ECoG: Electrocorticography, SWDs: Spike-and-wave discharges, SF: Saline formulation

In conditions such as epilepsy, ischemia, and hypoglycemia, increased expression of SGLT1 and SGLT2 proteins in the plasma membrane of neurons may play a protective role when energy supply decreases (e.g., during ischemia and hypoglycemia) or when energy consumption increases, during epilepsy.[8,9] A study by Melo et al.[13] lends support to this situation. They showed that inhibition of SGLT by phlorizin increased the severity of pilocarpine-induced limbic seizures, and neurodegeneration in the hippocampus increased 24 hours after seizures were created.[13] Similarly, absence seizures were observed to increase after SGLT2 inhibition with high doses of dapagliflozin in the present study. The inhibition of SGLT2 with high doses of dapagliflozin may have increased absence seizures by causing less glucose entry to the cell.

Under physiological conditions, dapagliflozin exhibits partial BBB permeability, achieving brain/plasma ratios of approximately 30-50%.[18]

Pathological conditions like epilepsy can impair BBB integrity, potentially increasing central nervous system drug penetration.[28,29] In WAG/Rij rats, PTZ-induced seizures have been shown to elevate both BBB permeability and SWDs activity.[30] In this context, enhanced brain access of high-dose dapagliflozin may have resulted in excessive SGLT2 inhibition or metabolic imbalance, promoting neuronal hyperexcitability and absence seizures. Conversely, low-dose administration may have maintained homeostasis, attenuating oxidative stress and inflammation without inducing energy deficit

Oxidative stress and neuroinflammation are increasingly recognized as key contributors to epileptogenesis in absence epilepsy. Elevated oxidative markers and increased lipid peroxidation have been reported in WAG/Rij rats compared to non-epileptic controls.[31,32] Additionally, pro-inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor-α have been shown to exacerbate SWD occurrence, while targeting inflammatory pathways (e.g., IL-6 inhibition) attenuates seizure activity.[33,34]

Recent studies suggest that SGLT2 inhibitors possess anti-inflammatory and antioxidant properties. Liu et al.[9] demonstrated that dapagliflozin (10 mg/kg) attenuated microglial activation and oxidative injury in a pilocarpine epilepsy model 9. Similarly, Abdelaziz et al.[35] showed that empagliflozin reduced lipid peroxidation and enhanced antioxidant defenses while modulating neuroplasticity pathways (brain-derived neurotrophic factor-tropomyosin receptor kinase B) in PTZ-induced seizures. Consistent with these findings, our results suggest that low-dose dapagliflozin (1 mg/kg) may have suppressed absence seizure activity by ameliorating oxidative stress and neuroinflammation, although direct molecular analyses were not conducted in this study. Future investigations incorporating biomarker assessments will be essential to confirm these proposed mechanisms.

Moreover, dapagliflozin has been reported to enhance dopamine levels and improve motor function in experimental Parkinson's models.[12] Considering that dopaminergic deficits are implicated in the pathophysiology of absence epilepsy and that dopamine agonists reduce, while dopamine antagonists exacerbate SWDs, it is possible that low-dose dapagliflozin exerted beneficial effects via dopaminergic modulation as well.

CONCLUSION

This study provides the first preclinical evidence that dapagliflozin, a selective SGLT2 inhibitor, exerts dose-dependent and bidirectional effects on absence seizure activity in a genetic model of epilepsy. The findings emphasize the critical role of dosage in modulating seizure susceptibility. Furthermore, the lack of data regarding SGLT2 expression and function in thalamocortical circuits, which are the central pathways involved in absence seizures, highlights an important area for future investigation.

Ethics

Ethics Committee Approval: In this study approved by Gaziantep University Animal Experiments Local Ethics Committee (approval no: 2019 HADYEK-57, date: 22.02.2020).

Informed Consent: Animal experiment.

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

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