Acıbadem Univ. Sağlık Bilim. Derg. 2024; 15 (2)
https://doi.org/10.31067/acusaglik.1347853

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Neurosicence / Sinirbilim

Gender-Specific Effects of Chronic Y-27632 Administration on Spike-And-Wave Discharges in Genetic Absence Epilepsy Rats

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Received: 25.08.2023
Accepted: 29.04.2024

ABSTRACT

Purpose: The acute intracerebroventricular (i.c.v.) injection of a Rho kinase inhibitor Y-27632 has beendemonstrated to reduce the spike-and-wave discharges (SWDs) in male GAERS (Genetic Absence Epilepsy Rats from Strasbourg) by our previous study. The purpose of this research is to determine the chronic use of five days will effect the SWDs of absence epilepsy in female GAERS and to compare the expression of SWDs between female and male GAERS.

Methods: Five female and male GAERS (150-350 g) were used in experiments. Stereotaxic surgery was performed to insert EEG recording electrodes over the fronto-parietal cortices. Female GAERS were injected with Y-27632 intraperitoneally over the five days,and compared to the baseline EEG of the same animals. SWD characteristics were analyzed using EEG recordings and analyzed.

Results: Total and mean SWD duration, and the number of SWDs did not significantly differ female GAERS, received Y-27632. Although a trend of reduced total duration was observed in female rats, it was not statistically significant. A significant difference was observed for the mean duration and number of SWDs between the female and male GAERS, ($p<0.05$). While the mean duration for SWDs is shorter in duration in females ($p=0.01$), the number of SWDs were more in females in comparison to male GAERS ($p=0.02$).

Conclusion: Although some outcomes did not reach statistical significance, trends suggest potential gender-related differences in SWD response to Y-27632 or SWD expression. The administration may not be as effective in intraperitoneal route as in i.c.v. Further experiments can be performed by changing the route of administration.

Keywords: GAERS, SWDs, ROCK, Y27632, female

ÖZET

Amaç: Bir Rho kinaz inhibitörü Y-27632'nin akut intraserebroventriküler (i.s.v.) enjeksiyonunun, erkek GAERS'lerde (Strasbourg'dan Genetik Absans Epilepsi Sıçanlar) diken-ve-dalga deşarjları (DDD'ler) azalttığı gösterilmiştir. Bu araştırmanın amacı, dişi GAERS'lerde, beş günlük kronik kullanımın absans epilepsisinin DDD'leri üzerindeki etkisini belirlemek, dişi ve erkek GAERS'ler arasındaki DDD'leri karşılaştırmaktır.

Yöntem: Deneylerde beş adet dişi ve erkek GAERS (150-350 g) kullanıldı. EEG kayıt elektrotlarının fronto-parietal kortekslere yerleştirilmesi için stereotaksik cerrahi uygulandı. Dişi GAERS'lere beş gün boyunca intraperitoneal olarak Y-27632 enjekte edildi ve aynı hayvanların bazal EEG'leri ile karşılaştırıldı. DDD'lerin özellikleri EEG kayıtları kullanılarak analiz edildi.

Bulgular: DDD'lerin toplam ve ortalama süresi ve sayısı, Y-27632 alan dişi GAERS'de anlamlı farklılık göstermedi. Dişi sıçanlarda toplam DDD süresinde azalma eğilimi görülmesine rağmen bu istatistiksel olarak anlamlı değildi. Dişi ve erkek GAERS'ler arasında DDD'lerin ortalama süresi ve sayısı açısından anlamlı bir fark gözlendi ($p<0,05$). Dişi GAERS'lerde ortalama DDD süresi daha kısa iken ($p=0,01$), DDD sayısı dişilerde erkeklere göre daha fazlaydı ($p=0,02$).

Sonuç: Sonuçlar istatistiksel anlamlılığa ulaşmasa da, Y-27632'ye verilen DDD yanıtında cinsiyete bağlı potansiyel farklılıklar olduğunu göstermektedir. Olasılıkla intraperitoneal yol, i.s.v. kadar etkili olmayabilir. Uygulama yolu değiştirilerek daha ileri deneyler planlanmaktadır.

Anahtar Kelimeler: GAERS, DDD'ler, ROCK, Y27632, dişi

Generalized absence seizures are a type of non-convulsive seizure characterized by unconsciousness and bilateral spike-and-wave discharges (SWDs) on EEGs (1). These seizures are prevalent across various idiopathic generalized syndrome categories and are often studied using animal models to understand their underlying mechanisms and develop relevant treatments (2, 3). Genetic rat models like GAERS and WAG/Rij rats are highlighted as valuable tools for replicating the persistent clinical manifestations of absence epilepsy, enhancing the accuracy of research outcomes compared to pharmacological models (4, 5). Many different mechanisms are discussed to underlie the pharmacology and pathophysiology of the seizures in the absence epilepsy (6-11).

We specifically investigated Rho kinase inhibitors in our previous studies. The role of RhoA and Rho-kinase in dendrite development and branching, as well as their involvement in neuronal cell survival and glutamate transmission, is well-known (12). The Rho kinase inhibitor Y-27632 is mentioned for its potential in preventing glutamate-induced cell death (13). Fasudil and Y-27632 have been shown to be protective as well, on retinal excitotoxicity caused by NMDA-induced damage, focusing on their influence on RhoA and ROCK2 levels and cell survival (14). In epilepsy research, Y-27632 and fasudil decreased myoclonic jerks, clonic convulsions, tonic hindlimb extensions, tonic convulsion index, and recovery latency while increasing Rho translocation in brain homogenates of PTZ-treated mice (15). Previously we have shown that single systemic dose of Y-27632 reduced absence seizure duration, while fasudil lowered seizure frequency (16). Local brain administration exhibited a comprehensive suppressive impact on total seizure duration, seizure count, and average individual seizure length with Rho kinase inhibitors, but intraperitoneal administration did not show that strong results (16).

Sex differences are observed not only in humans but also in animal models like rats (17). Neglecting to consider both sexes in research can lead to incomplete understanding of drug effects and cognitive capacities, therefore the research involving both genders are encouraged to prevent possible adverse effect in a certain population (18). A study by Prendergast et al. highlights the importance of including both sexes for valid and applicable research outcomes (19). Certain types of epilepsy subtypes also might have varying susceptibilities based on gender (20, 21). Neglecting the sex differences in the research called scientists to call the National Institutes of Health into action, to prevent adverse effects of the drugs faced mostly among women by being inclusive in the animal research in terms of including female gender as well (18).

Existing literature suggests that different outcomes such as histopathological changes, behavioral effects, molecular responses, and the development of epilepsy might be influenced by seizures during development in ways that are specific to sex, age, and brain regions (22). The sex differences in these genetic absence epilepsy models have also been discussed and although no differences of seizure expressions were found (4), hormonal changes during pregnancy, the effect of sex hormones as well as epidemiological data shows the gender may influence the possible pharmacotherapies (23). Therefore, in this study, we aimed to investigate if the chronic intraperitoneal administration of Rho kinase inhibitor Y-27632 in female rats will show differential results in terms of SWD expression in comparison to male GAERS rats, as well as to investigate the baseline expression of SWDs between female and male GAERS.

Material and Methods

Animals and experimental design

The experimental procedures were conducted on adult female and male Genetic Absence Epilepsy Rats from Strasbourg (GAERS) rats, aged 3 to 4 months and weighing between 150 and 350 grams (n=5;5= 10), sourced from the breeding colony of the Department of Pharmacology and Clinical Pharmacology at Marmara University School of Medicine. Additionally, male adult Wistar rats, derived from male and female rats with previously recorded EEGs demonstrating the absence of spike-and-wave discharges (SWD) activity, were employed. They were obtained from the Experimental Research Animals Unit of Marmara University Faculty of Medicine (DEHAMER).

The rats were housed individually in cages within a temperature-regulated environment set at 21 ± 3°C, with a 12-hour light/dark cycle (lights on at 8 a.m.). Adequate provisions of food and water were available ad libitum to the rats throughout the study. All experimental protocols involving animals were subject to approval by the Ethical Committee for Experimental Animals at Marmara University, with the assigned protocol number 28.2017. MAR. These procedures were conducted in compliance with the guidelines outlined in the EU Directive 2010/63/EU governing animal experimentation. The group name for the basal recordings from the female and male rats were tagged as; Baseline-FM and Baseline-M; respectively. And the group name for the Y27632-injected rats were tagged as; Y27632-FM.

Stereotaxic surgery

The animals underwent anesthesia induction using ketamine (100 mg/kg, intraperitoneal, Alfamine 10%; Alfasan International B.V.) and xylazine (10 mg/kg, intraperitoneal, Alfazyne 2%; Alfasan International B.V.). Subsequently, they were securely positioned within a stereotaxic frame (Stoelting Model 51600, Stoelting Co., Illinois, USA). A longitudinal incision was carefully made on the skull to expose the underlying tissue. Four stainless steel screws, affixed with insulated wires, were bilaterally implanted onto the frontoparietal cortex to facilitate cortical EEG recordings. Each cortex recorded is represented by the potential difference between the two electrodes on the same side, for instance the potential difference of the right parietal electrode and the right frontal electrode is the right cortex recording. The connections between the electrodes and the insulated wires were established, leading to a micro connector designed for the purpose of EEG data acquisition. To ensure stability and proper positioning, both the electrodes and the wires were protected by dental acrylic and affixed firmly to the skull.

EEG recordings, drug injections and analysis

After the stereotaxic surgery, the animals were allowed to recover for a week. One week later, 3 h of baseline activity was recorded on EEG (09:00-12:00). Two days later the chronic injections began, the Rho kinase inhibitor Y-27632 was purchased from (Tocris Bioscience (UK). The dose of 0.3 mg/kg was dissolved in saline and injected according to the body weight of each animal.

On the fifth day following the last injection 3 h EEG recordings from the GAERS was recorded. The Y27632 was injected to female rats twice daily for the 5 days, and the last day following injections the EEG recordings were performed. SWD complexes, which are usually identified if the duration is longer than 1 s, with a train of sharp spikes and subsequent slow waves (7-11 Hz) and the amplitude of at least twice the background amplitude of the EEG, were analyzed. EEG was amplified through a BioAmp ML 136 amplifier, with an anti-aliasing filter set at 0.1-125 Hz and digitized at a sampling rate of 1,000 Hz. The data were analyzed using Chart v7 program (PowerLab 8/35, ADI Instruments, Oxfordshire, UK).

Statistical analysis

All statistical analyses were performed with GraphPad Prism version 9.1.0 (GraphPad Software, San Diego, USA). For statistical analysis of the EEG data in the female GAERS that received Y27632, the total number of SWDs, mean duration of each individual; as well as the number of SWDs, a paired t-test was conducted to assess the significance of the observed differences. The obtained t-value, degrees of freedom (df) and the corresponding two-tailed p-value was provided, p-value less than 0.05 has been shown with an asterisk (*). For the comparison of the female and male baseline SWD parameters of GAERS groups an unpaired t-test (two-tailed) was performed. The data is represented as t(df) = t-value, p = p-value for t-tests.

Results

The effect of intraperitoneal injection of Y-27632 on the total duration of SWDs in female GAERS groups

The total duration of SWDs (s) in the groups of Baseline-FM and Y27632-FM showed no statistical significance, although closer to p<0.5 value. The paired t-test comparing baseline EEG and the Y-27632 injected GAERS, showed total duration of the SWDs in the female rats showed overall less duration although statistically not significant; t(4) = 1.75, p = 0.08 (Fig 1).

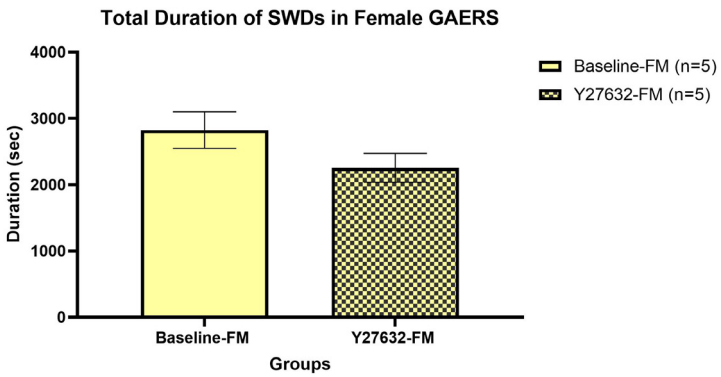


Figure 1: Impact of Intraperitoneal Y-27632 Injection on Total SWD Duration in Female GAERS Rats. *The graph depicts assessing the effect of intraperitoneal injection of Y-27632 on the total duration of SWDs within female GAERS groups. Analysis of the total SWD duration (s) in the Baseline-FM and Y27632-FM groups did not yield statistically significant differences, although the results approached a p-value of less than 0.5.*

The effect of intraperitoneal injection of Y-27632 on the mean duration and the number of SWDs in female GAERS groups

The mean duration of SWDs (s) in the groups showed no statistical significant difference. Y27632-FM group expressed less duration for each individual seizures in comparison to the Baseline-FM (t(4) = 0.2, p = 0.85; p=0.01; Fig 2A). On the other hand, the number of SWDs in the female groups showed decreased number of SWDs (t(4) = 1.85, p = 0.13; Fig 2B).

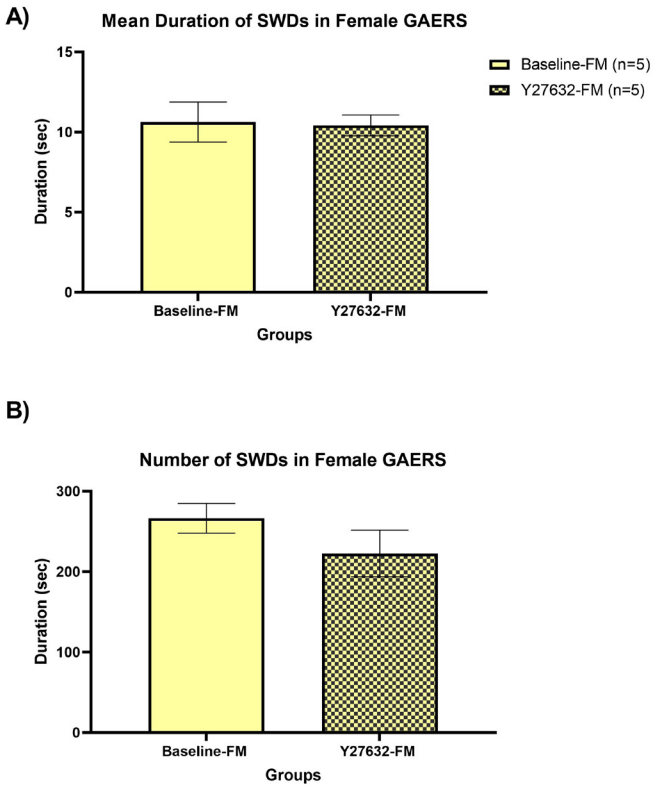


Figure 2: Effect of Intraperitoneal Y-27632 Injection on Mean SWD Duration and SWD Numbers in Female GAERS Rats. (A) The number of SWDs within the female groups indicated an elevated count, although the difference did not achieve statistical significance. (B) Analysis of the mean SWD duration (s) across the groups revealed no statistically significant differences. The Y27632-FM group exhibited less duration for individual seizures in contrast to the Baseline-FM group. Data are presented as mean ± standard error of the mean (SEM). *p < 0.05, ns = not significant.

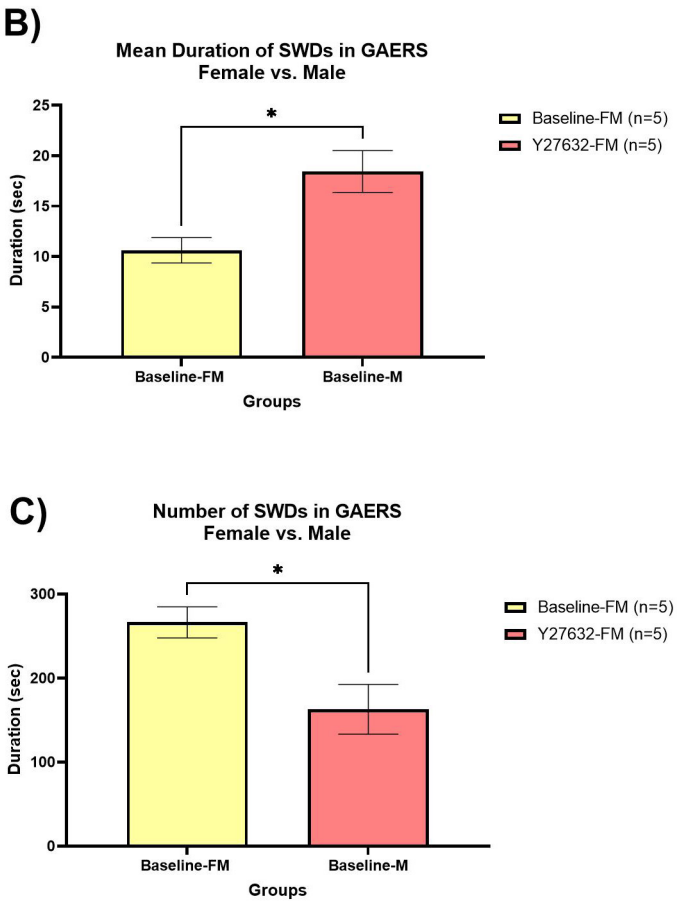
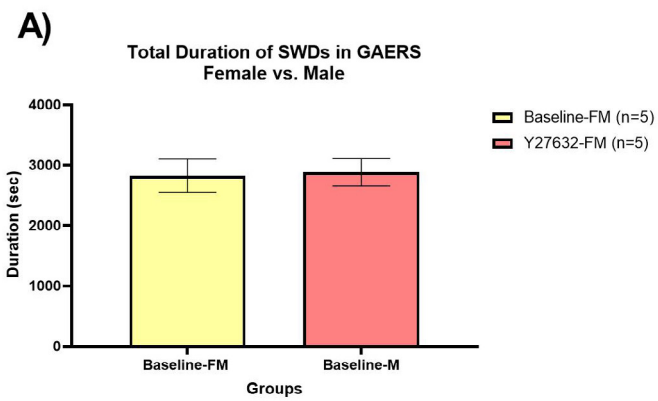


Figure 3: Comparison of SWD Parameters in Female and Male GAERS Rats. (A) Total duration of SWDs did not show a statistically significant difference between female and male GAERS rats. (B) Mean SWD duration, with females displaying significantly shorter mean durations compared to males. (C) the number of SWDs exhibited significant variation between female and male GAERS rats, with females manifesting a greater number of SWDs relative to males. Data are presented as mean ± standard error of the mean (SEM). *p < 0.05, **p < 0.01, ns = not significant.

The SWD parameters between the female and male GAERS groups



An unpaired t-test was conducted to assess the significance of the total duration, mean duration and number of SWDs between female and male GAERS baseline SWDs. Although there was no statistically significant difference for the total duration ($t(8) = 1.62$, $p = 0.14$; Fig 3A), there were differences between the female and male GAERS for the mean duration and number of SWDs ($p < 0.05$). While the mean duration for SWDs is shorter in duration in females ($t(8) = 3.23$, $p = 0.01$; Fig 3B), the number of SWDs were in females in comparison to male GAERS ($t(8) = 2.97$, $p = 0.02$; Fig 3C).

Discussion

The present study aimed to investigate the potential differential effects of chronic intraperitoneal administration of the Rho kinase inhibitor Y-27632 on SWD parameters in the female GAERS in comparison to their own baseline EEG. As well as to study if there are any gender-based differences between the baseline SWD parameters of female and male GAERS. Previously we have shown that the intracranial administration of these Rho kinase inhibitors; Fasudil and Y-27632 (16), inhibits SWD parameters such as total duration, mean duration and number of SWDs in male GAERS.

Our previous study was not inclusive in terms of gender. In light of this background, the study used GAERS rats of both sexes to explore the impact of Y-27632 administration on SWD expression. The results indicated that the total duration of SWDs did not show statistically significant differences between the experimental groups, although female rats exhibited a trend towards reduced SWD duration. Most literature on the pharmacological and neurological research on the epileptic models revolves around male gender (24, 25), except few studies (26, 27). The issues around the hormonal influence of SWDs in adulthood, as well as menstrual cycles have been an issue related to the research on the animals in our previous studies which we only implemented on male GAERS (10, 11, 26, 28, 29). The finding of no significant differences in terms of seizure expression shows that female GAERS can also be implemented as a consistent model for absence epilepsy research.

Furthermore, in this study, our results showed that although there are no statistically significant differences in the overall expression of the total duration between the female and male GAERS, the mean duration and the number of SWDs were different between the groups. Although the average duration of SWDs is briefer in females, there exists a higher count of SWDs in females as opposed to male GAERS. This observation raises the possibility of gender-associated variations in the manifestation of SWD characteristics. Nevertheless, additional investigations are required, encompassing diverse colonies of GAERS and other genetic models of absence epilepsy such as Wistar Albino Glaxo/Rijswijk (WAG/Rij), to gain a deeper understanding of these potential gender-related distinctions.

In conclusion, this study contributes to the growing body of knowledge regarding gender-specific responses to epilepsy treatment. However, it is important to interpret these results with caution and consider potential confounding factors. The investigation into the effects of Rho kinase inhibitor Y-27632 on SWD expression in GAERS rats provides insights into potential sex-related differences in response to this pharmacological intervention. While some results did not achieve statistical significance, the trends observed underscore the importance of considering gender-based factors in epilepsy research and treatment. Further investigations with larger sample sizes and extended experimental durations could provide a more comprehensive understanding of the intricate relationship between gender, pharmacological interventions, and the absence epilepsy outcomes.

Conclusion

This study sheds light on potential gender-related differences in the response to chronic intraperitoneal administration of the Rho kinase inhibitor Y-27632 in female GAERS. While certain outcomes did not reach statistical significance, the trends observed suggest the existence of gender-based variations in SWD characteristics and response to pharmacological intervention. In addition, this study underscores the importance of considering gender-related factors in epilepsy research and treatment strategies. Further investigations involving larger cohorts and extended experimental durations are warranted to comprehensively unravel the intricate interplay between gender, pharmacological interventions, and absence epilepsy outcomes.

Declarations

Funding

This study had no external funding.

Conflicts Of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval

This study was approved by the Ethical Committee for Experimental Animals at Marmara University, with the assigned protocol number 28.2017.MAR.

Availability Of Data And Material

Data are available upon request from the corresponding author.

Authors' Contributions

MY and FO conceptualized and designed the study. MY, GG, DAT and İAY organized the database, performed the statistical analysis, and wrote the first draft of the manuscript. MY, İAY, GG, DAT, GB, and BBA performed the stereotaxic surgery, drug injections and EEG recordings, analysis. MY, FO and İAY contributed to the manuscript's revision and read and approved the submitted version. All authors approved the final version of the manuscript. We want to thank for our technician Nurettin Demirci for his help for the sustaining of GAERS breeds.

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