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Gender-Dependent Differences in Motor Activity, Anxiety and Depression-Like Behavior are Preserved in Spontaneously Hypertensive Rats with Epilepsy

Natasha M Ivanova, Zlatina P Nenchoska, Daniela M Pechlivanova and Jana D Tchekalarova*

Institute of Neurobiology, Bulgarian Academy of Sciences, Sofia, Bulgaria

Abstract

Objectives: Preclinical and clinical studies have shown gender differences regarding motor activity, depressive and anxiety behavior. Gender distinctions could be interfered by chronic stress, pain, depression, epilepsy. Depression and anxiety are main types of affective disorders identified in epileptic patients. Over the last years, animal models have been widely used to study the neurobiological and genetic base of those affective disorders. The aim of the present study was to explore the role of gender and kainate treatment on emotional behaviors depression and anxiety in spontaneously hypertensive rats.

Methods: Status epilepticus was induced in freely moving rats by repetitive intraperitoneal injections of kainate in low subconvulsive doses. The development of chronic epileptic stage was confirmed by the presence of spontaneous motor seizures detected by 24 h video-monitoring. Control and experimental groups were tested in the sucrose preference test, open field test, and elevated plus maze two months after kainate treatment.

Results: Although female rats were more vulnerable to status epilepticus than male hypertensive rats, they showed decreased spontaneous seizures during the chronic epileptic phase. Epilepsy produced a depression-like behavior in both genders, which showed anhedonia-like behavior during the light and the dark phases, though higher affinity to sucrose was preserved in females. Both epileptic male and female spontaneously hypertensive rats were hyperactive than naïve rats but gender difference was still present in the open field test. Gender difference was detected between the controls and kainate-treated groups in the elevated plus maze test, as male rats were less anxious than females indicated by the increased time spent in the open arms.

Conclusion: Male spontaneously hypertensive rats exhibited higher seizure susceptibility than female rats in the kainate model of temporal lobe epilepsy, while gender-dependent behavioral differences in naive rats were preserved during the chronic epileptic phase.

Keywords: Kainate model; Temporal lobe epilepsy; Spontaneous motor seizures; Behavior; Depression; Anxiety; Spontaneously hypertensive rats

Introduction

Preclinical and clinical studies have shown gender differences regarding motor activity, depressive and anxiety behavior [1]. Clinical studies reported that women are twice more likely to suffer from depression than men [2]. Gender distinctions could be interfered by chronic stress, pain, depression, epilepsy, etc. [3]. Depression and anxiety are the main types of affective disorders identified in epileptic patients [4].

Different studies have shown that spontaneously hypertensive rats are useful model for investigation of the behavioral changes associated with brain disorders, including epilepsy [5-7]. In this study, we found gender differences in seizure susceptibility that provoke us to explore further whether behavioral differences between naïve male and female spontaneously hypertensive rats are preserved in epileptic rats.

In this study we aimed to explore the role of gender and kainate treatment on depression and anxiety in spontaneously hypertensive rats.

Materials and Methods

Male and female spontaneously hypertensive rats at two months of age were kept under standardized conditions (T° 21 ± 2°C, 50-60% humidity) and housed in a 12 hr light/dark cycle with a regular pellet diet ad libitum. The experiments were carried out in accordance with the guidance and general recommendations of the Local Ethics Committee of the Institute of Neurobiology, registration № 92/11.03.2019, Bulgarian Academy of Sciences on the use of laboratory animals.

The protocol of kainate-induced status epilepticus was executed according to Hellier et al. [8] and is described earlier [5,7]. In brief, SE was induced by repetitive injections of KA (Abcam, UK) starting with a dose of 5 mg/kg, i.p. (1 ml/kg) at the first hour of observation. Thereafter, KA was administered in half of the above-mentioned dose (2.5 mg/kg) every half an hour. Seizure intensity was evaluated by a modified Racine's scale [5,7]. The number of seizures of class III, IV or V were registered and used as a criterion for an additional KA injection. The severity of the seizures and the well-being of each rat was assessed to determine whether the next dose of KA should be half (2.5 mg/kg) or omitted. Video-monitoring (24 h/day for 12-14 weeks starting 24 h after SE) was accomplished using an infrared-sensitive

***Corresponding author:** Institute of Neurobiology, Acad G. Bonchev Str.,Bl. 23, Bulgaria, Academy of Sciences, Sofia 1113, Bulgaria; Tel. 359-2-979-2172; Fax: +359-2-8719-109; E-mail: janetchecalarova@gmail.com

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colored camera (S- 2016, AVTECH, Taiwan, no. AVC307R) connected to a computer. The recordings were visually analyzed by independent observers to detect SRSs of class IV or V. Partial seizures of class I and II were not detected by video monitoring because without simultaneous EEG recording they could easily be omitted. The sucrose preference test, the open field and the elevated plus maze were conducted two months after *status epileptius* as previously described [7]. Four groups of animals were tested: C-male (male control group); KA-male (male group treated with kainate); C-female (female control group); KA-female (female group treated with kainate). Sucrose preference (C-male n=5; KA-male n=26; C-female n=9; KA- female n=8) was expressed as the percentage of the volume of sucrose solution of the total volume of fluid (sucrose plus regular water) consumed during a 12-h period (light phase- 8:00-20:00 h and dark phase- 20:00-8:00 h, respectively). The calculated measures were as follows: in the open field test (C-male n=13; KA-male n=15; C-female n=8; KA- female n=9): total distance travelled; in the elevated plus maze test (C-male n=15; KA-male n=26; C-female n=8; KA- female n=14) (cm): time spent in open arms versus total time (%). The behavior was recorded using an infrared sensitive CCD camera and a video tracking system (SMART PanLab software, Harvard Apparatus, USA).

Statistical analysis

Two-way ANOVA followed by post-hoc Mann-Whitney was applied. P<0.05 was accepted as an index of significant difference.

Results

Male rats were more resistant to development of a kainate-induced SE and needed lower dose than female rats (*p=0.049) (Table 1). However, they exhibited shorter latency to onset of SE (*p=0.001) and higher frequency of spontaneous motor seizure (*p=0.028) than female rats during the light period (Table 1). A tendency for higher seizure frequency in male than female rats was also detected during the dark period.

	Average	Median	SD	Range
Dose of KA required to induce SE (mg/kg) SHR-male	22.71 ± 1.44	25.000	7.068	27.500
SHR-female	17.25 ± 0.69* Mann-Whitney U Statistic= 68.500 T=123.500 (P=0.049)	17.500	2.189	5.000
Latency to onset of the first spontaneous seizure (days) SHR-male	15.34 ± 1.83	13.000	10.404	51.000
SHR-female	42 ± 2.7* Mann-Whitney U Statistic= 11.000 T=364.(P=<0.001)	41.000	8.524	23.000
Average frequency of SRS during the 3rd month (light phase): SHR-male	52.08 ± 17.49	26.000	60.587	202.000
SHR-female	14 ± 3.37* T=43.500 (P=0.028)	11.000	8.926	89.000
Average frequency of SRS during the 3rd month (dark phase): SHR-male	10.46 ± 6.69	0.750	24.130	89.000
SHR-female	2.28 ± 0.6	2.00	1.604	4.00

*p<0.05 male vs. female rats.

Table 1: Characteristics of status epilepticus (SE) and spontaneous recurrent seizures (SRS) in SHR-male and SHR-female in kainate model of temporal lobe epilepsy

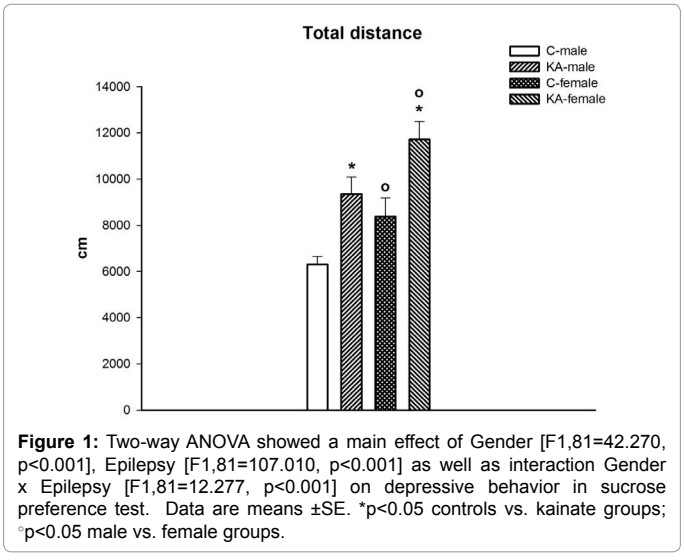

Figure 1: Two-way ANOVA showed a main effect of Gender [F1,81=42.270, p<0.001], Epilepsy [F1,81=107.010, p<0.001] as well as interaction Gender x Epilepsy [F1,81=12.277, p<0.001] on depressive behavior in sucrose preference test. Data are means ±SE. *p<0.05 controls vs. kainate groups; °p<0.05 male vs. female groups.

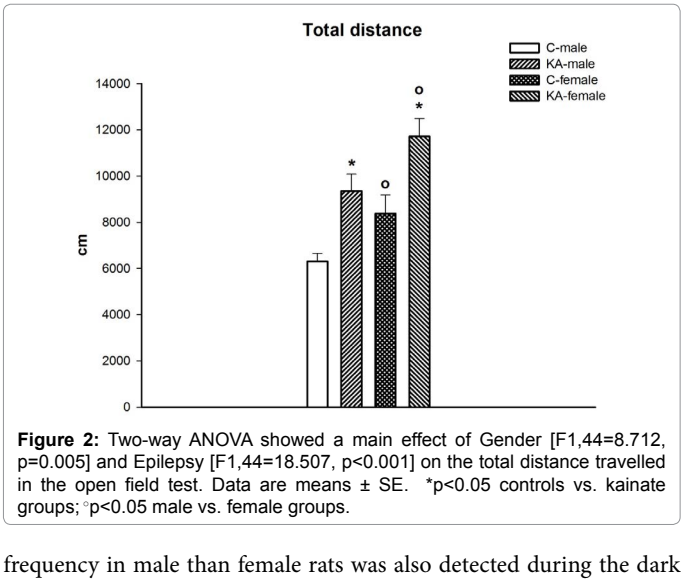

Figure 2: Two-way ANOVA showed a main effect of Gender [F1,44=8.712, p=0.005] and Epilepsy [F1,44=18.507, p<0.001] on the total distance travelled in the open field test. Data are means ± SE. *p<0.05 controls vs. kainate groups; °p<0.05 male vs. female groups.

The control female rats exhibited a higher affinity to sucrose than male rats without diurnal variations (°p<0.05) (Figure 1). Both male and female epileptic rats showed an anhedonia-like behavior during the light and the dark phase though higher affinity to sucrose was preserved in females (*p<0.05).

Both epileptic genders were hyperactive compared to controls (*p<0.05) (Figure 2). Like controls, epileptic female rats showed higher activity than male SHRs (°p<0.05). Control and epileptic males were less anxious than females and showed increased time spent in the open arms (°p<0.05) (Figure 3).

Discussion

Our results showed a remarkable difference in the emotional behavior between male and female spontaneously hypertensive rats both in physiological and pathophysiological conditions. As this strain is commonly used to model attention deficit hyperactivity disorder (ADHD) our experimental data are in line with a gender difference described for patients with ADHD [9]. Behavioral gender differences

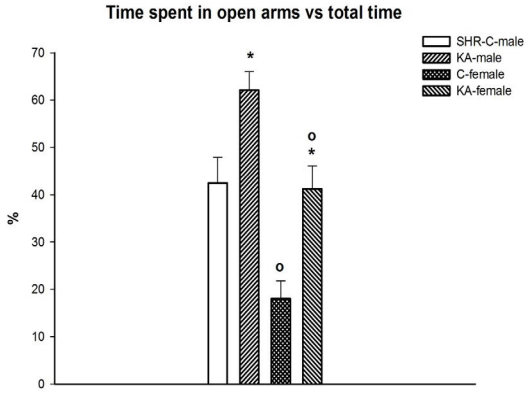

Figure 3: Two-way ANOVA showed a main effect of Gender [F1,62=18.621, p<0.001] and Epilepsy [F1,62=16.672, p<0.001] on ratio of time spent in the open arms vs. totoal time spent in the elevated plus maze test. Data are means ± SE. *p<0.05 controls vs. kainate groups; °p<0.05 male vs. female groups.

in this strain were observed by different investigators. Fedra et al. showed that female SHRs are characterized by hyperactivity compared to male rats [10] while methylphenidate enhances ethanol intake in females SHRs [11]. The observed depressive-like behavior in both male and female spontaneously hypertensive rats is consistent with our previous report, where males demonstrated a depressive-like behavior in the sucrose preference test and forced swimming test five months after SE [12]. However, in the present study, male and female epileptic hypertensive rats demonstrated an anhedonia during the light phase while the kainate-treated females exhibited a less pronounced depressive-like behavior than male rats during the dark phase. This result disagrees with clinical data [2]. However, it might suggest that comorbidity between ADHD and epilepsy modeled by spontaneously hypertensive rats is important for gender associated differences in emotional behavior. Co-morbidity between ADHD and epilepsy was described in clinical and experimental conditions [13,14]. Our previous findings focused mainly on male spontaneously hypertensive rats revealed that biochemical, electrophysiological and behavioral characteristic of naive and epileptic hypertensive rats are similar to that of epileptic Wistar rats supporting the suggestion that spontaneously hypertensive rats could be used to model co-morbidity between ADHD and epilepsy.

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