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The effect of duloxetine on ECoG activity of absence-epilepsy model in WAG/Rij rats

Absans epilepsi modeli olan WAG/Rij sıçanlarda duloksetinin ECoG aktivitesi üzerine etkisi

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Abstract

Introduction: Many epidemiological studies have found a high incidence of depression and anxiety in people with epilepsy. Duloxetine is a selective inhibitor of serotonin and norepinephrine reuptake (SNRI) and commonly prescribed in a patient with major depressive disorder. The aim of this study was to investigate the effect of duloxetine on the WAG/Rij rat in an experimental rat model of absence-epilepsy.

Methods: WAG/Rij rats were randomly assigned into 5 groups with 7 animals in each group. Tripolar electrodes were placed on the skull to perform electrocorticography (ECoG) evaluation. Then, following the recovery period, ECoGs were recorded at 09:00 am for 3 hours every day. Subsequently, duloxetine (1, 5, 10 and 30 mg/kg) was injected intraperitoneally (i.p). After the treatment program, ECoG recordings were taken for 3 hours. And then all animal anxiety-like behavior by using the behavioral test, open field test (OFT) was performed after duloxetine (1,5,10 and 30 mg/kg) treatment. The total number and the total duration of the spike-wave discharges (SWDs) were calculated offline. The number of squares crossed (locomotor activity) and the duration of grooming episodes were analyzed in OFT.

Results: The doses of duloxetine (1 mg/kg) did not alter ECoG and OFT parameters. The 5, 10 and 30 mg/kg doses of duloxetine decreased the total number and the total duration of SWDs, ($p<0.05$) and increased the number of squares crossed when compared to with control group ($p<0.05$) without changing duration of grooming episodes ($p>0.05$). Intraperitoneal administering of 1 mg/kg duloxetine did not show any statistically significant change in regard to the number and duration of SWDs.

Discussion and Conclusion: In the present study, duloxetine reduce dose-dependent absences-like seizures and anxiety-like behavior.

Keywords: Absence epilepsy; duloxetine; ECoG; open field test; WAG/Rij rat.

Özet

Amaç: Birçok epidemiyolojik çalışma epilepsili hastalarda yüksek depresyon ve anksiyete insidansı olduğunu bulmuştur. Duloxetin, serotonin ve norepinefrin geri alımının seçici bir inhibitörüdür (SNRI) ve genellikle majör depresif bozukluğu olan hastalara reçete edilir. Bu çalışmanın amacı, absans-epilepsinin deneysel bir hayvan modeli olan WAG/Rij sıçanlarda epileptiform aktive üzerine duloksetinin etkisini araştırmaktır.

Gereç ve Yöntem: WAG/Rij sıçanlar her grupta 7 hayvan bulunan 5 gruba rasgele ayrıldı. Elektrokortikografi (ECoG) değerlendirmesi yapabilmek için kafataslarına tripolar elektrotlar yerleştirildi. Daha sonra, iyileşme periyodunu takiben, her sabah saat 09:00'da üç saat bazal ECoG kayıtları alındı. Sonrasında, duloksetin (1, 5, 10 ve 30 mg/kg) intraperitoneal (i.p) enjekte edildi. Tedavi programı sonrası, ECoG kaydı 3 saat boyunca alındı. Daha sonra tüm hayvanların anksiyete benzeri davranışları davranışsal test olan açık alan testi (AAT) ile test edildi. Diken dalga deşarjlarının (DDD) toplam sayısı ve toplam süresi hesaplandı. Geçilen karelerin sayısı (lokomotor aktivite) ve grooming bölümlerinin süresi AAT'de analiz edildi.

Bulgular: Duloksetin (1 mg/kg) dozları ECoG ve AAT parametrelerini değiştirmedi. İntraperitoneal 1 mg/kg duloksetin uygulaması, DDD'lerin sayısı ve süresi açısından istatistiksel olarak anlamlı bir değişiklik göstermedi. 5, 10 ve 30 mg/kg duloksetin dozları kontrol grubuyla karşılaştırıldığı zaman DDD'lerin toplam sayısını ve süresini azalttı, ($p<0.05$) ve grooming süresini değiştirmeksizin geçilen karelerin sayısını arttırdı.

Sonuç: Sunulan çalışmada, duloksetinin, doza bağımlı olarak absans benzeri nöbetleri ve anksiyete benzeri davranışları azalttığı görüldü.

Anahtar Sözcükler: Absans epilepsi; açık alan testi; duloksetin; ECoG; WAG/Rij sıçan.

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Epilepsy is a complex and common neurological disorder that affects about 50 million epilepsy patients in the World, which constitutes 2-3% of all Word population.[1] Depression is also considered one of the most important causes of poor quality of life in people with epilepsy.[2] Comorbid depression and anxiety disorders in a patient with epilepsy are common. Previous studies demonstrated that 11-25% suffered from anxiety and 9-37% of patient with epilepsy suffered from depression.[3,4] A lot of studies showed that depression has been associated with an increased risk of seizures in a patient with epilepsy.[5] Previous clinical and experimental studies suggest that seizures severity associated with the choice of antidepressant drugs and dose prescribed in a patient.[6,7] Furthermore, older antidepressants such as imipramine, amitriptyline, and bupropion were reported to decrease the seizure threshold in a patient with epilepsy.[5] Selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) are commonly the prescribed antidepressants in a patient with depression and epilepsy to treat depression, because of their less risk of seizure.[5]

Duloxetine is a potent SNRI and is used in the treatment of female stress urinary incontinence, peripheral diabetic neuropathic pain, fibromyalgia, generalized anxiety disorder and major depression. A lot studies demonstrated the proconvulsant and anticonvulsant effect of duloxetine in various experimental study.[6–8]

Rats of the Wistar Albino Glaxo/Rijswijk rats (WAG/Rij) strain display spontaneous SWDs morphologically similar to human absence seizures.[9] Also, many experimental studies demonstrated that WAG/Rij rats exhibit depression-like behavioral symptoms.[10]

The aim of this study was to investigate the relationship between dose-like seizure and anxiety-depression in WAG/Rij rats.

Materials and Method

Animals

Six-month-old male 35 WAG/Rij rats were used in this study. All animals were under kept in controlled environmental conditions (50±8% humidity, 21±1°C; a 12-hour/12-hour light/dark cycle; lights on at 06:00–18:00 hour) and a sound attenuated room. Rats were allowed free access to food (standard laboratory chow) and water until the time of experiments. The experimental protocol was approved by the Ethical Committee of Tokat Gaziosmanpaşa University and procedures involving animals and their care was conducted in accordance with the European Union Directive 2010/63/EU.

Experimental design

WAG/Rij rats were assigned into 5 groups with 7 animals in each group randomly.

(Group 1); WAG/Rij rats received saline (4 ml/kg/i.p).

(Group 2); WAG/Rij rats received duloxetine (1 mg/kg/i.p).

(Group 3); WAG/Rij rats received duloxetine (5 mg/kg/i.p).

(Group 4); WAG/Rij rats received duloxetine (10 mg/kg/i.p).

(Group 5); WAG/Rij rats received duloxetine (30 mg/kg/i.p).

Drugs and drug administration

Ketamine hydrochloride and xylazine hydrochloride were purchased from Sigma Chemical Co and duloxetine taken from the local pharmacy. Duloxetine was dissolved in sterile physiologic saline. The doses of the drugs were determined in accordance with previous studies.[6,7]

Experimental absences epilepsy model in WAG/Rij rats

Implantation of the electrode for ECoG recording

Rats were fasted 1 day before the operation. Stereotactic surgery was performed under intraperitoneal (i.p.) ketamine and xylazine (90 and 10 mg/kg, respectively) anesthesia. The membrane on the bone tissue was cleared and the detected reference point (bregma). Tripolar electrodes were placement in rat skull for ECoG recording. Tripolar electrodes were placement in the coordinates described as follows; positive electrode in the frontal cortex (AP 2 mm; L 3.5 mm), negative electrode in the parietal area (somatosensory cortex, AP-6 mm; L 4 mm) and reference electrode over the cerebellum Electrodes were permanently fixed to the skull with cold dental acrylic together with additional two stainless steel screws.[11,12] After the surgery, animals housed in individual cages and kept alone in order to prevent damages of the electrode. All animals were allowed to recover seven days before ECoG recording (Fig. 1).

Electroencephalogram recording

After 7 days of healing, rats were habituated to the in a registration cage (26×18×42 cm) and the electrode fixed to the rat skull was connected to the recording apparatus with a cable. Basal ECoG recordings were taken for 3 hours (between 09:00 and 12:00 AM) performed using the acknowledge software (version 3.8) and the MP150 multi-channel physiological analysis system (BioPac Systems Inc.; USA) from freely moving animals in a noise-isolated room. Duloxetine was administered (i.p.) in different doses at 1, 5, 10 and 30 mg/kg rate separately and then ECoG recordings were taken for 3 hours (between 09:00 and 12:00 AM). The number, duration, and amplitude of spike-wave discharges (SWDs) in the recordings were used for evaluating the seizures (Fig. 2).

Evaluation of anxiety- depression-like behaviors in WAG/Rij rats

Open field test

After the duloxetine injection and 180 min ECoG recording, the beginning of the open field test. The test was performed in a white Plexiglas square field (100x100 cm square arena divided into 64 equal segments) with 30 cm high walls. Rats were habituated to the test room for seven days. The WAG/Rij rat was initially put in the center of the open field and its

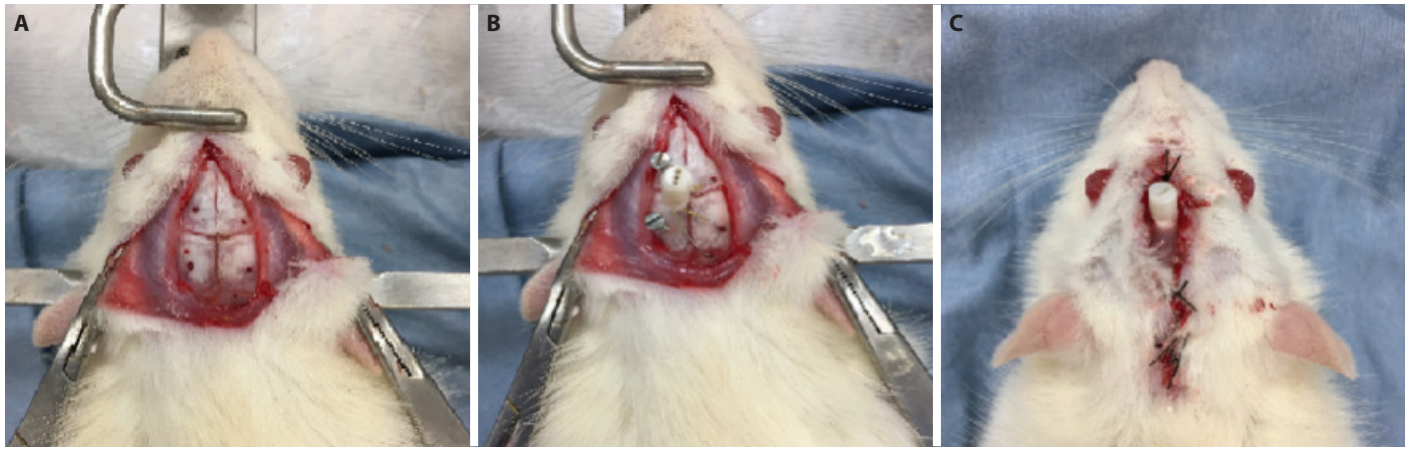

Figure 1. (A) Animals were fixed in the stereotaxic instrument; then micro-drilling of the skull, the electrodes, and stainless screw were inserted on skull. **(B)** Cold acrylic screws and electrodes were fixed and the scalp was sutured.

activity was video recorded for 5 min with a video camera. The following parameters were analyzed: the number of squares crossed (locomotor activity) and the duration of grooming episodes. At the start of each test, the apparatus was cleared with 90% alcohol. Each animal was tested only once. Decreased locomotor activity, a number of rearings and duration of grooming were considered as an indicator of anxiety-like behavior.

Statistical analysis

All data were analyzed using GraphPad Prism 7 (Software, Inc., La Jolla, CA) and SPSS Version 22.0 (IBM Corp). Paired-Samples T-test was applied between two dependent groups in comparison with baseline records of the WAG/Rij groups. All groups were compared by one-way analysis of variance (ANOVA) followed by post hoc test Tukey. Data were expressed as mean±standard error of the mean (SEM) for every group's data. For all comparisons, the accepted criterion for the level of significance was set at $p<0.05$.

Results

The total number and duration of SWDs in ECoG recordings were calculated. The total numbers of SWD's for a 3-h epoch were 129±19 and 120±14 with a total duration of 878±22 and 840±18 sec; in the control and sham groups, respectively. There was no statistically significant change between the control and sham groups ($p>0.05$).

Intraperitoneal administering of 1 mg/kg duloxetine did not display statistically important change both the number and duration of SWDs. As shown in Figure 3, number and duration of SWDs in ECoG were 129±19 and 104±9 and 878±22 and 792±55 sec in control group (WAG/Rij rat) and 1 mg/kg duloxetine group, respectively. Intraperitoneal administering of 5, 10 and 30 mg/kg duloxetine significantly decreased both the number and duration of SWDs. As shown in Figure 3, the number and duration of SWDs in ECoG were 129±19; 84±8; 72±9 and 878±22; 672±67; 531±57 in control group (WAG/Rij rat), at doses of 5, 10 and 30 mg/kg duloxetine group, respectively.

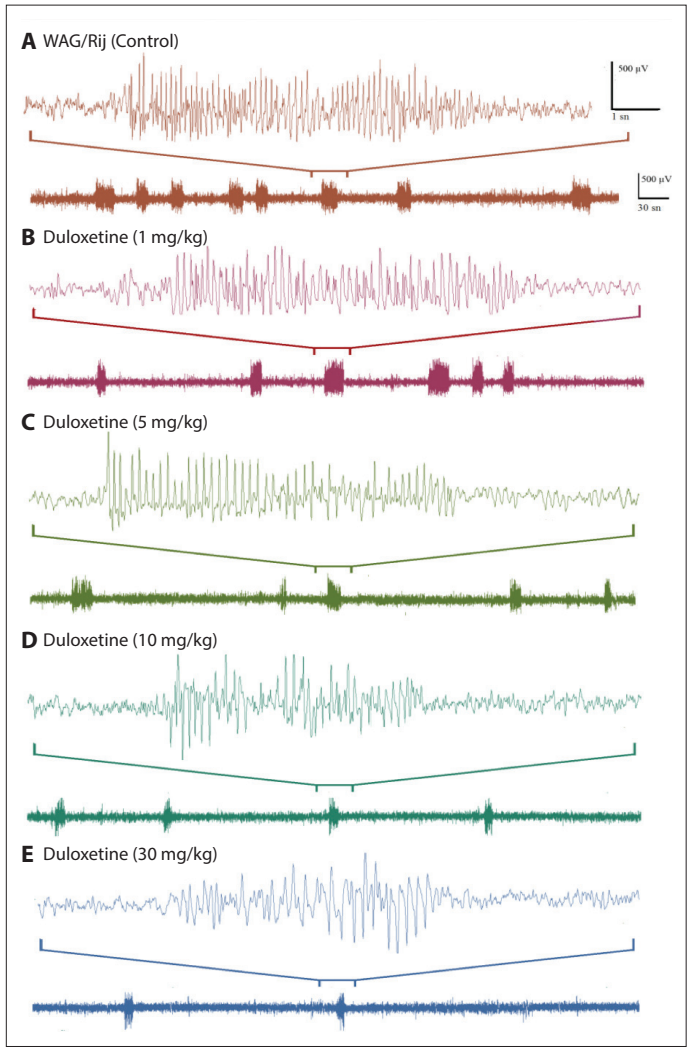

Figure 2. Representative ECoG recordings for all groups with; **(A)** WAG/Rij (Control); **(B)** Duloxetine (1 mg/kg), **(C)** Duloxetine (5 mg/kg), **(D)** Duloxetine (10 mg/kg), **(E)** Duloxetine (30 mg/kg). The 1 mg/kg dose of duloxetine did not show statistically important change both the number and duration of SWDs. 5, 10 and 30 mg/kg duloxetine significantly reduced both the number and duration of SWDs.

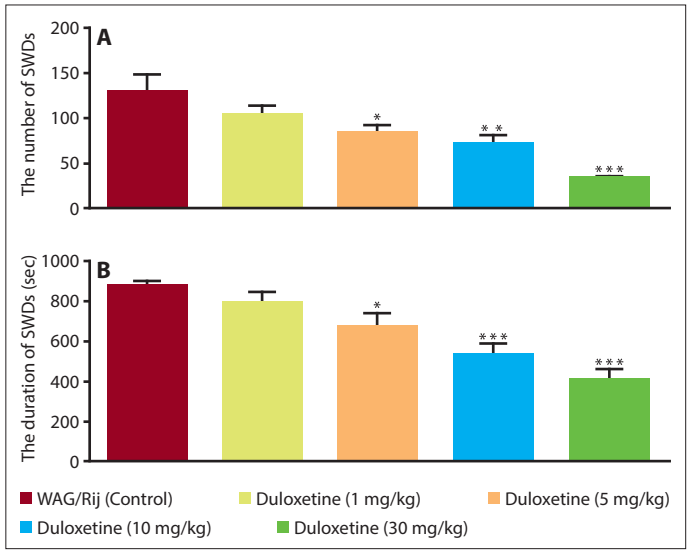

Figure 3. The effects of different doses of duloxetine (1, 5, 10 and 30 mg/kg) on the total number and total duration of SWDs in WAG/Rij rats with genetic absence epilepsy. 1 mg/kg (i.p.) duloxetine did change the total number and duration of SWDs in WAG/Rij rats compared to the control group ($p>0.05$). The 5, 10 and 30 mg/kg group duloxetine significantly reduced the total number and duration of SWDs compared to control group (*$p<0.05$; **$p<0.01$; ***$p<0.001$). The total number and duration of SWDs for 3-h epoch was significantly lower in at a dose of 30 mg/kg duloxetine group compared to the other duloxetine treatment groups.

30 mg/kg duloxetine was the most effective dose to decrease both the number and duration of SWDs.

Duloxetine effects in anxiety-like behavior paradigms

Open Field Test

Results obtained in the open field test, the number of squares crossed were 45±2; 40±2 and with the total duration of grooming 11.8±1.33 and 9±2.30 sec; in the control and sham groups, respectively. There was no statistically important change between the control and sham groups ($p>0.05$).

Intraperitoneal administering of 1 mg/kg duloxetine did not show statistically important change both the number of squares crossed and duration of grooming in OFT. As shown in Figure 4, the number of squares crossed and duration of grooming in OFT were 45±2 and 47±4 and 11.8±1.33 and 10.77±1.25 sec in control group (WAG/Rij rat) and 1 mg/kg duloxetine group, respectively. Intraperitoneal administering of 5, 10 and 30 mg/kg duloxetine significantly decreased the number of squares crossed; however, there was no statistically important change in the duration of grooming in OFT. As shown in Figure 4, number of squares crossed and duration of grooming were 45±2; 62±4; 66±9; 72±8; and 11.8±1.33; 12.00±1.73; 11.50±2.10; 13.38±1.57 in control group (WAG/Rij rat), at doses of 5, 10 and 30 mg/kg duloxetine group, respectively. 30 mg/kg duloxetine was the most effective dose to moderate anxiolytic properties in OFT.

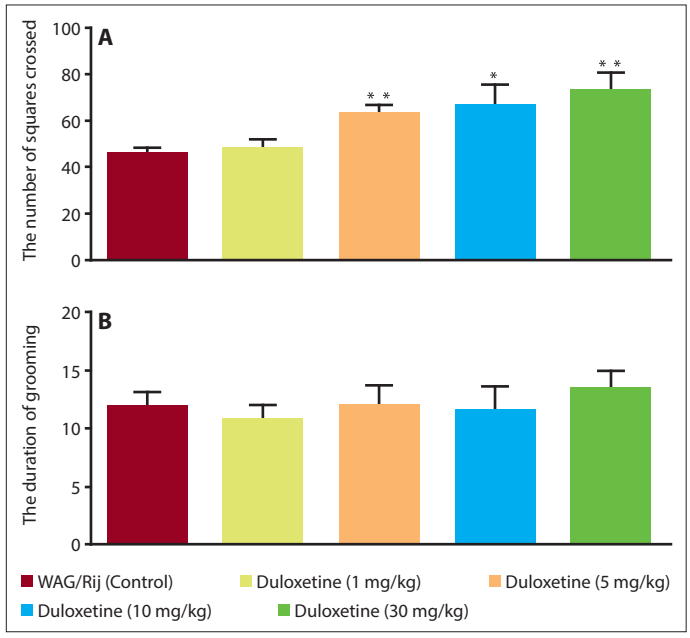

Figure 4. The effects of different doses of duloxetine (1, 5, 10 and 30 mg/kg) on the open field test measures in absence-epileptic WAG/Rij rat. **(A)** The number of squares crossed (locomotor activity). **(B)** The duration of grooming 1 mg/kg (i.p.) duloxetine did changed the number of squares crossed ($p>0.05$), but 5, 10 and 30mg/kg duloxetine importantly reduced number of squares crossed when compared to the control group (*$p<0.05$; **$p<0.01$; ***$p<0.001$). All doses of duloxetine did not alter the duration of grooming compared to the control group ($p>0.05$).

Discussion

In this study, the 5, 10 and 30 mg/kg injection of duloxetine dose-dependently reduced the number and duration of SWDs, also increased the number of squares crossed (locomotor activity) in OFT but did not change the duration of grooming compared to control group. The 1 mg/kg duloxetine did not significantly alter all parameters in ECoG recording and OFT test. The results of the present study indicate that duloxetine exerts a considerable antiepileptic and anxiolytic-like effect on absence-like seizures in WAG/Rij rats.

Many studies reported that the use of antidepressants in an epileptic patient is controversial because of increase in seizure severity, especially with older generations of drug.[5,13] Interestingly, a lot of studies reported that some of the newer antidepressants, such as serotonin and norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) exhibit anticonvulsant effect.[5,13] On the other hand, the possible antiepileptic effect of SNRIs has been scarcely studied. Venlafaxine (SNRI drug), showed anti-epileptic action, whereas high doses of venlafaxine exhibits an increased epileptiform activity, but high doses of venlafaxine (75 mg/kg or more) showed a proconvulsant effect.[14–16] The preliminary results in our study have indicated a possible role for the duloxetine in convulsive seizures. In this study, we showed that acute treatment of duloxetine injection of 1, 5, 10 and 30 mg/

kg increased epileptiform activity in penicillin-induced seizure model in the rat.[7] Recently a study reported that seizure-induced respiratory arrest and death was decreased in WT mice with duloxetine treatment in maximal electroshock-induced seizures in adult in mice.[17] Citraro et al. (2015) demonstrated that chronic treatment of duloxetine (10 and 30 mg/kg) decreased both number and duration of SWDs in adult WAG/Rij rats.[6] In this study, both of the number and duration of SWDs parameters were significantly decreased in 5, 10 and 30 mg/kg duloxetine treatment groups compared to control. However, both the number and duration of SWDs parameters did not alter in 1 mg/kg duloxetine treatment. The duloxetine (30 mg/kg) was found the most effective considering both the number and duration of SWD parameters of absence epilepsy.

Zomkowski et al. (2012) demonstrated that a dose range of 1–30 mg/kg duloxetine did not alter locomotor activity in OFT, but decreased immobility time in the forced swim test.[18] 30 mg/kg for duloxetine did not significantly change locomotion in the mouse formalin pain model.[19] On the other hand, Grégoire showed that 10 mg/kg duloxetine decreased anxiety-like behavior by increased locomotor activity in a model of neuropathic pain in rats.[20] Also, another study showed that duloxetine (5 mg/kg) increased center arena activity in OFT.[21] In this study, 5, 10 and 30 mg/kg duloxetine injection significantly increased locomotor activity, but 1 mg/kg duloxetine did not alter the number of squares crossed.

A new study demonstrated that 3.0 mg/kg duloxetine injection significantly elevated the extracellular concentration of dopamine prefrontal cortex and exhibits dopamine 1 receptor (D1)- like effect.[22] Sarkisova et al. reported that D1-like dopamine receptors were very lower in WAG/Rij rats compared with control rats.[23] In their study, they found a significant relationship between increased seizure and anxiety-depression-like behaviors. In the meantime, they observed an increase in seizure severity and anxiety-like behaviors in rats with low D1 levels. It was shown that hypofunction of the dopaminergic brain system responsible for depression-like behavior in WAG/Rij rats.[23] Many study demonstrated that dopamine antagonists increased number and duration of SWDs in WAG/Rij rats, while cocaine, apomorphine, and amphetamine (dopamine agonist drug) reduce the number and duration of SWDs.[24–27] When the literature is considered, the dose-dependent antiepileptic and anxiolytic effect of duloxetine treatment may be mediated by the dopamine-enhancing effect.

Conclusion

Depression is one of the most commonly only psychiatric disorder in people with epilepsy. Antidepressant drugs are the third class of drugs commonly used by patients with epilepsy.[28] The same antidepressant drug has different effects on different types of epilepsy. The present study was the first to investigate the effect of duloxetine on drug dose effect and anxiety-like behaviors in absence epilepsy in WAG/Rij rats. Although it is an animal study, it may be useful to use in patients with abscence epilepsy.

Conflict of interest: There are no relevant conflicts of interest to disclose.

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