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The effect of fluoxetine on penicillin-induced epileptiform activity

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ABSTRACT

Aim: Depression is the most frequent psychiatric comorbidity in patients with epilepsy. Fluoxetine is the most widely used selective serotonin reuptake inhibitor (SSRI) in depression. The aim of the present study was to evaluate the dose-dependent effect of fluoxetine on penicillin-induced seizure by electrocorticogram (ECoG), a model for simple partial epilepsy.
Method: The epileptiform activity was induced by intracortical (i.c.) microinjection of penicillin into the left sensorimotor cortex. Thirty minutes after penicillin injection, 5, 10, or 20 mg/kg doses of fluoxetine were administered intraperitoneally (i.p.). An ECoG recording was performed for 180 min using the data acquisition system. The frequency and the amplitude of the epileptiform activity were analyzed.
Results: Penicillin induced bilateral spikes and spike–wave complexes within 2–5 min. The 5 and 10 mg/kg doses of fluoxetine significantly reduced the frequency (58%, $p < 0.05$ and 69%, $p < 0.01$, 40 and 50 min after fluoxetine injection, respectively) and amplitude (60%, $p < 0.01$ and 73%, $p < 0.05$, 40 and 120 min after fluoxetine injection, respectively) of epileptiform activity compared with penicillin-induced seizure group (control). Five-milligram fluoxetine (i.p.) was the most effective dose to decrease frequency and amplitude on penicillin-induced epileptiform activity. However, a higher fluoxetine dose (20 mg/kg) significantly increased frequency (147%, $p < 0.01$) and amplitude (123%, $p < 0.05$) of epileptiform activity 40 and 120 min after fluoxetine administration compared with control group. Also, bursts of population spikes were seen in 20 mg/kg fluoxetine doses.
Conclusion: Results of the present study indicate that low and moderate fluoxetine doses have an anticonvulsant effect while high doses have proconvulsant effect on penicillin-induced epileptic activity.

1. Introduction

Epilepsy is one of the most common and heterogeneous neurological disorders and is characterized by abnormal and synchronous neuronal discharge within the brain [1,2]. It affects around 50 million people worldwide (1–3% of world population), and about 400,000 new epilepsy diagnoses are made each year [3,4]. Depression is one of the most frequent psychiatric comorbidity in patients with epilepsy [5]. About two-thirds of patients with epilepsy experience depression [6,7]. Suicide risk is ten times higher in patients with epilepsy compared with the general population [8,9]. A clinical study by Dale Hesdorffer showed a bidirectional relationship between depression and epilepsy. Besides, the author suggested that there were common pathophysiological mechanisms underlying epilepsy and depression and that patients with psychiatric disorders had a two- to sevenfold higher risk for developing epilepsy [10]. Therefore, it is necessary to treat depression and reduce the risk of suicide in patients with epilepsy using antidepressants [11,12]. However, the presence of concomitant depression in patients diagnosed to have epilepsy causes even greater concern. Previous studies have shown that antidepressant treatment for a patient with epilepsy increases the risk for relapsing of the condition [13], triggers the onset of seizures, and aggravates preexisting epilepsy [14]. Since epilepsy and depression commonly appear in the same patient, it is important to know whether the antidepressant used to treat depression has anticonvulsant or proconvulsant properties. Nevertheless, conventional antidepressants (tricyclic antidepressants and bupropion) when added to the treatment regime decrease the seizure threshold in patients with epilepsy. Administering tricyclic antidepressants such as imipramine or amitriptyline was reported to increase seizure frequency in patients with epilepsy, leaving depression untreated. Although previous clinical and experimental studies showed that the use of new generation antidepressants such as serotonin noradrenaline reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) has considerably less effect on seizures, their use in patients with epilepsy is controversial [15]. Different experimental and clinical studies dealing with the effect of SSRI and SNRI antidepressants on epileptiform activity are needed.

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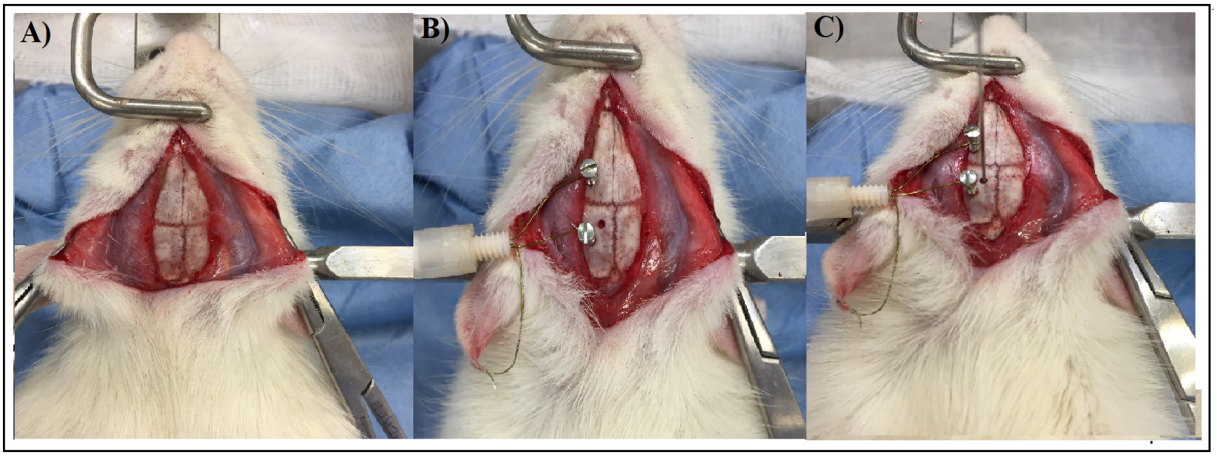

Fig. 1. A) Rat skulls after tendons and fascia were removed. B) Small holes were drilled at certain coordinates with the help of microdrill. Localization of steel screws at determined coordinates for ECoG recording are shown. Steel screws were connected to positive or negative electrodes while the skin surface was connected to the ground electrode. C) Intracortical administration of penicillin by stereotaxic instrument.

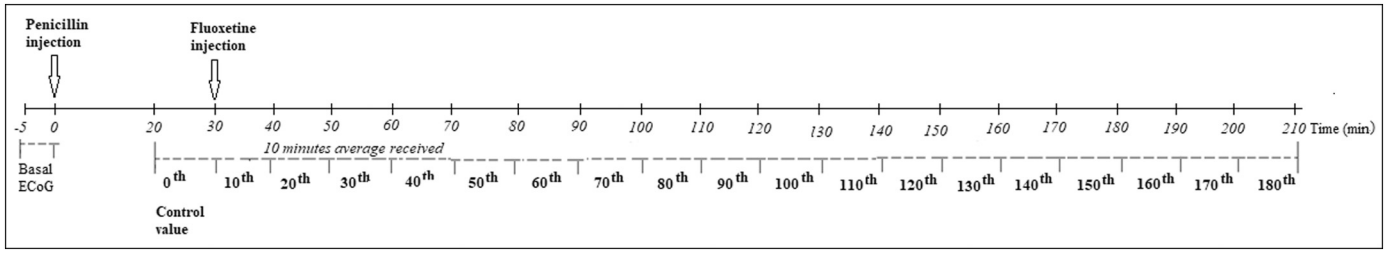

Fig. 2. Experimental timeline. Last 10 min of the first 30-minute period after penicillin administration (from 20th to 30th minute) was taken as an initial point (control). For percentage calculations, the sum of spike number in this 10-minute period was divided by 10, and obtained value was considered 100%. Total number of spikes between 30th and 40th minutes were taken as 10th minute values while those from 40th to 50th minutes were taken as 20th minute ones. This pattern was used throughout the experiment, and ECoG recording analysis of 210 min was completed.

Fluoxetine is a SSRI and is widely used as an antidepressant drug. Clinical and animal studies demonstrated that caution should be taken when using fluoxetine for antidepressant treatment in patients diagnosed with epilepsy and concomitant depression [16,17]. Some clinical studies demonstrated that fluoxetine use exerts an anticonvulsant effect in patients with epilepsy [18,19]. However, Prasher [17] reported a case in which fluoxetine treatment induced seizures. The effect of fluoxetine on epilepsy was investigated in animal studies. Anticonvulsant activity of fluoxetine has been shown in focally induced limbic motor seizures in rats [20], in a pilocarpine-induced chronic model of epilepsy [21], audiogenic seizures in rats and mice [22,23], maximal electroshock-tonic extension in rats [24], and 4AP-induced epileptiform activity in rats [25]. The proconvulsant activity of fluoxetine has been revealed in genetically epileptic rats [26], pilocarpine-mediated status epilepticus rats [27], and kindling epileptic rats [28]. Recently Li et al. showed the proepileptogenic effects of chronic fluoxetine treatment in kindling epileptogenesis in mice [29].

Although the effect of fluoxetine on epileptiform activity has been shown in many experimental epilepsy models and clinical studies, there are no studies dealing with its effect in simple partial epilepsy. Penicillin-induced experimental epilepsy model was used in the present study to investigate the acute effects of fluoxetine on simple partial epilepsy. To our best knowledge, this is the first study investigating the effect of fluoxetine on seizures.

2. Materials and methods

2.1. Animals

Twenty-eight male, adult Wistar rats (three-month-old, 200–250 g) obtained from Experimental Research Centre of Tokat Gaziosmanpasa University were used. All experimental procedures were carried out based on the principles set in the European Union Directive (2010/63/EU) and Turkish Legislation about animal experiments. The study protocol was approved by the Ethics Committee of the Tokat Gaziosmanpasa University for Animal Experimentation of the National Institute, Tokat (HAYDEK, 2018/37). Rats were housed as four per cage (40 × 40 × 20 cm) under a 12 h dark and 12 h light cycles (lights on at 07.00), at room temperature (21–23 °C), relative humidity (60 ± 15%), and with food pellets and water provided ad libitum. Rats

Fig. 3. Original trace showing ECoG activity in all groups. A) Baseline ECoG activity before injection of penicillin and fluoxetine. B) The intracortical injection of 500 units of penicillin induced epileptiform activity on ECoG. C) The intraperitoneal administration of fluoxetine (5 mg/kg i.p.) significantly decreased mean frequency and amplitude of penicillin-induced epileptiform activity 40 min after fluoxetine injection. D) The administration of fluoxetine (10 mg/kg i.p.) significantly decreased mean frequency and amplitude of epileptiform activity 50 and 120 min after fluoxetine injection, respectively. E) Administration of fluoxetine (20 mg/kg i.p.) significantly increased mean frequency and amplitude of epileptiform activity 40 and 120 min after fluoxetine injection, respectively. Fluoxetine (20 mg/kg i.p.) even led to the development of status epilepticus-like activity.

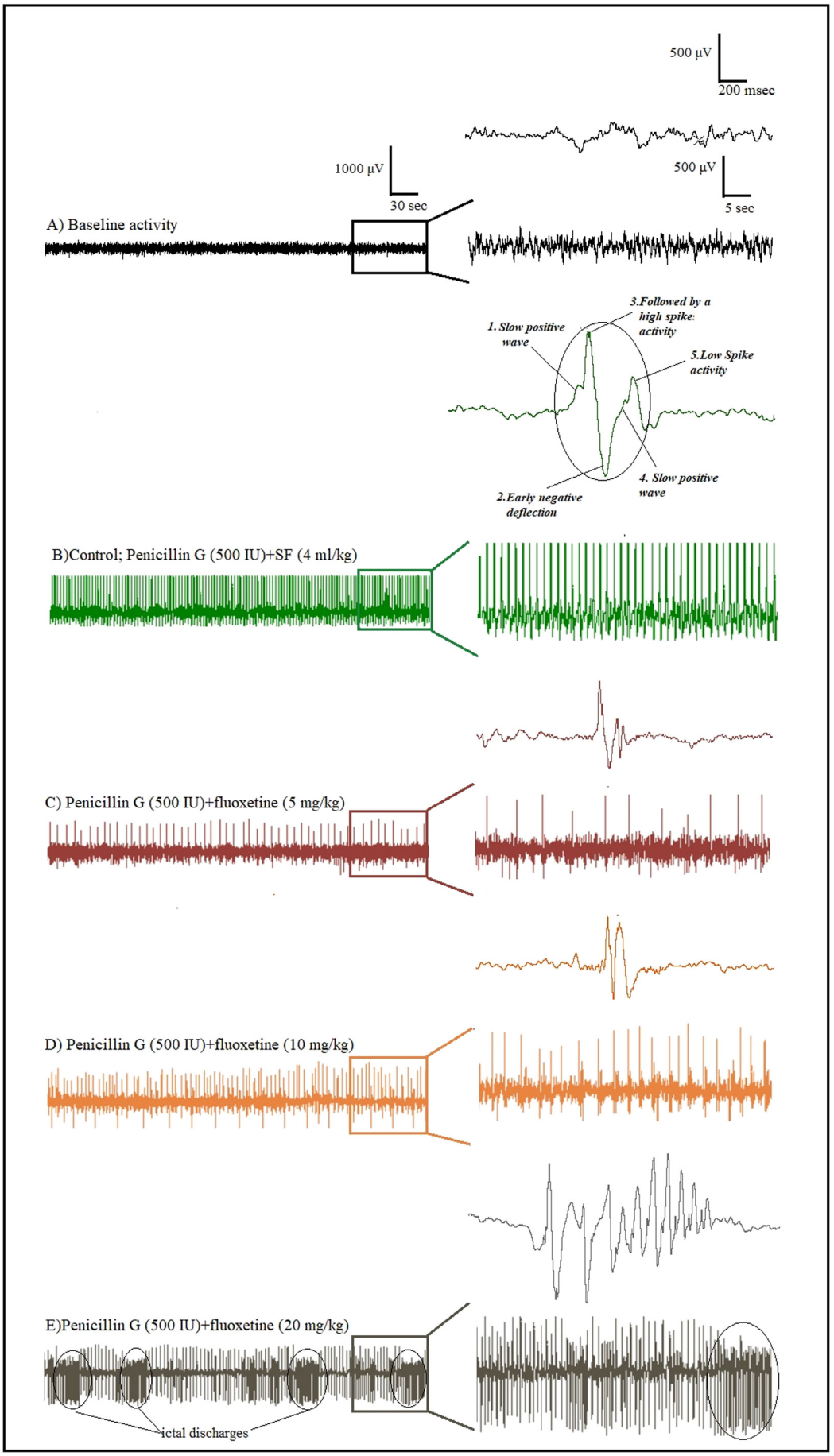
500 µV
200 msec
1000 µV
30 sec
500 µV
5 sec
A) Baseline activity
3.Followed by a high spike activity
1. Slow positive wave
5.Low Spike activity
4. Slow positive wave
2.Early negative deflection
B)Control; Penicillin G (500 IU)+SF (4 ml/kg)
C) Penicillin G (500 IU)+fluoxetine (5 mg/kg)
D) Penicillin G (500 IU)+fluoxetine (10 mg/kg)
E)Penicillin G (500 IU)+fluoxetine (20 mg/kg)
ictal discharges

Table 1
Spike frequency (spike/min) of penicillin-induced epileptiform activity.

Groups	0th (control value)	40th	50th	90th	120th	180th
Control (SF, 0.5 ml/kg)	47 ± 2	46 ± 3	49 ± 3	47 ± 3	46 ± 4	43 ± 3
Fluoxetine (5 mg/kg)	45 ± 1	26 ± 7*	25 ± 8*	13 ± 4***	18 ± 5***	4 ± 0.5***
Fluoxetine (10 mg/kg)	45 ± 4	43 ± 3	31 ± 4*	24 ± 1***	21 ± 1***	20 ± 1***
Fluoxetine (20 mg/kg)	43 ± 2	63 ± 9*	65 ± 5**	85 ± 7***	72 ± 7**	75 ± 8***

Values are given as mean ± SEM.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

were divided randomly into four groups so that each group had seven rats. Four groups had one of the following treatments:

(1) 500 IU penicillin (2.5 μl, intracortical (i.c.)) + 4 ml/kg sterile physiologic saline (intraperitoneally (i.p.));
(2) 500 IU penicillin (2.5 μl, i.c.) + 5 mg/kg fluoxetine (i.p.);
(3) 500 IU penicillin (2.5 μl, i.c.) + 10 mg/kg fluoxetine (i.p.);
(4) 500 IU penicillin (2.5 μl, i.c.) + 20 mg/kg fluoxetine (i.p.).

2.2. Surgical procedure and electrocorticogram (ECoG) recordings

The surgical procedure employed was based on the protocol previously described by our group [2]. The rats were starved for one day before the operation. On the day of the surgical procedure, rats were anesthetized i.p. using 1.25 g/kg urethane. Assessment of loss of righting reflex was performed by pressing rats' foot, and the level of anesthesia was assessed. Then, rats were placed in a stereotaxic instrument. Small burr holes of 1 mm were opened in the skull using a microdrill without damaging the dura mater. Bleeding, which might occur in bone tissue during the process, was prevented by bone wax (W810, ETHICON). Rectal temperature was maintained between 36.0 and 37 °C via an electric blanket-controlled heating system (Harvard 7087). Stainless steel screw was implanted on the dura mater over the left somatomotor cortex. Then, copper wires of the tripolar electrode were wrapped around the stainless steel screw. Electrode coordinates were the following: the first screw (first electrode) 3 mm lateral to sagittal suture and 4 mm rostral to bregma; the second screw (second electrode) 3 mm lateral to sagittal suture and 4 mm caudal to bregma as previously described [2,30]. The ground electrode was implanted over the rat skin (Fig. 1). A PowerLab 16/35 data acquisition system was used to continuously monitor ECoG activity.

2.3. Drug administration and induction of epileptiform activity

Fluoxetine (Sandoz Pharmaceutical Industry, Turkey) was used in the experiments. Penicillin G potassium and urethane were purchased from Sigma Chemical Co. Fluoxetine doses of 5, 10, or 20 mg/kg were used in the experiment. Fluoxetine doses were decided based on previous studies [20,25,27].

Fluoxetine was dissolved in sterile physiologic saline and injected (i.p.) in 1 ml volume. Penicillin was dissolved in sterile physiologic saline, and injections (i.c.) were administered into the left somatomotor cortex of each rat through a stereotaxic instrument with the coordinates of 3 mm caudal to the bregma, 3 mm lateral to sagittal sutures, and 3.2 mm ventral to the surface of the skull based on the atlas of the rat brain [31,32].

In the penicillin group (control), the epileptic focus was produced by 500 units of penicillin G potassium injection (3.2 mm beneath the brain surface by a Hamilton microsyringe type 701N; infusion rate 0.5 μl/min) [2]. Within 2–5 min, epileptic seizures occurred in ECoG. Then, the frequency and amplitude of epileptiform activity reached a stable level within 25–30 min, and this activity lasted for 4 h.

In the penicillin + fluoxetine groups, epileptiform activity was induced with 500 units of penicillin G potassium injection (i.c.). Thirty minutes after penicillin (i.c.) injection, fluoxetine at 5, 10, or 20 mg/kg doses were administrated (i.p.). After the injection of fluoxetine, ECoG recordings were taken for 3 h (Fig. 2).

2.4. Statistical analyses

Results are given as means ± standard error of the mean (SEM). SPSS software (ver. 17.0) was used for statistical analyses. Normality of the results was tested with one-sample Kolmogorov–Smirnov test. All data were normally distributed. One-way ANOVA was performed to compare the study groups. Post hoc Tukey–Kramer test was employed for multiple comparisons.

3. Results

Baseline ECoG activities of each animal were recorded before the i.c. penicillin injection (Fig. 3A). Penicillin injection (500 units) into cortex induced an epileptiform activity within 2–4 min, which was characterized by bilateral spikes and spike–wave complexes. As shown in Fig. 3B, bilateral spikes and spike–wave complexes developed in the order of first as a slow positive wave followed by early negative deflection, a high spike activity, slow positive wave, and low spike activity. It reached a stable level in terms of frequency and amplitude within 30 min, which continued for 3–5 h. Fluoxetine was injected 30 min after penicillin injection (Fig. 3B).

Intraperitoneal fluoxetine of 5 mg/kg importantly decreased the mean frequency and amplitude of epileptiform activity 40 min after fluoxetine administration. As shown in Tables 1 and 2, mean frequency and amplitude in ECoG were 46 ± 3 and 26 ± 7 spike/min and 840 ± 50 and 493 ± 81 μV in control (penicillin, 500 IU) and

Table 2
Spike amplitude (μV) of penicillin-induced epileptiform activity.

Groups	0th (control value)	40th	50th	90th	120th	180th
Control (SF, 0.5 ml/kg)	872 ± 27	840 ± 50	825 ± 51	788 ± 50	823 ± 58	776 ± 59
Fluoxetine (5 mg/kg)	819 ± 34	493 ± 81**	483 ± 70**	439 ± 63***	395 ± 51***	305 ± 47***
Fluoxetine (10 mg/kg)	849 ± 44	774 ± 40	701 ± 42	650 ± 33	620 ± 35*	573 ± 37**
Fluoxetine (20 mg/kg)	887 ± 27	911 ± 85	967 ± 39	914 ± 31	1089 ± 63*	1107 ± 80*

Values are given as mean ± SEM.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

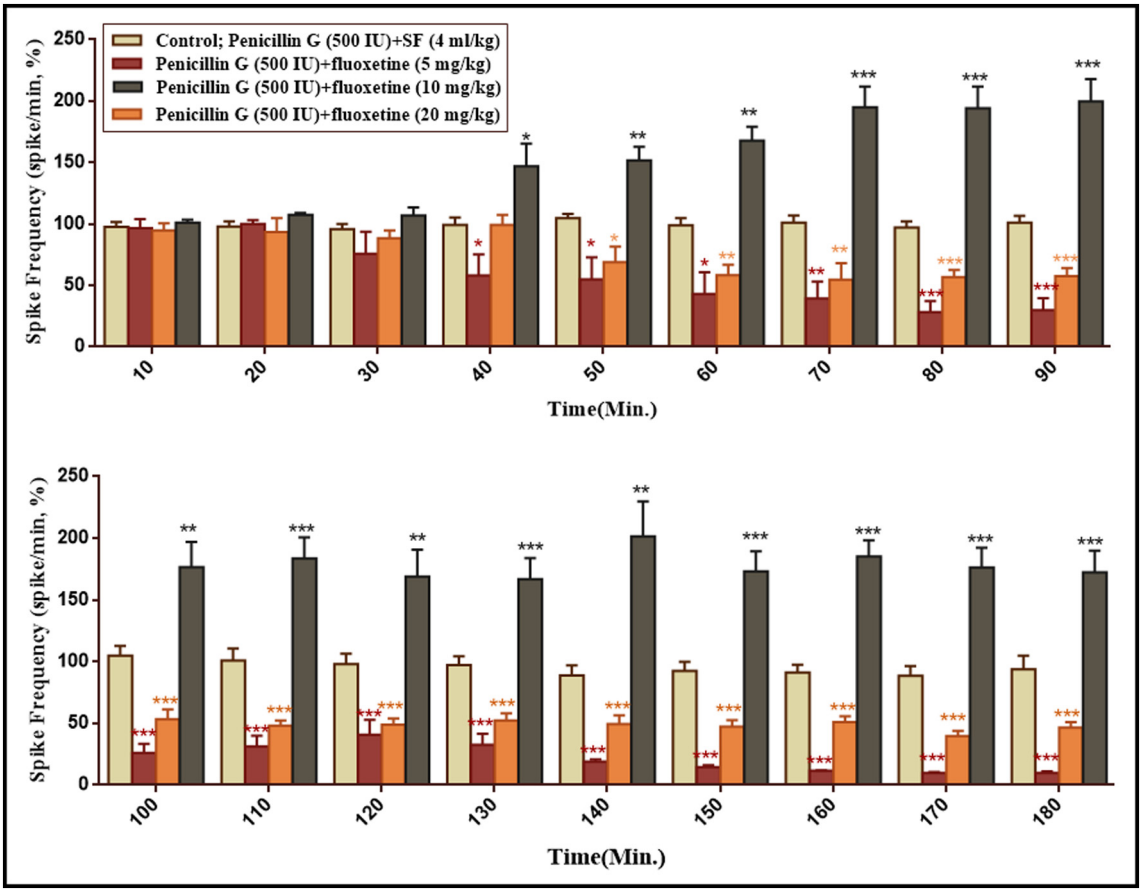

Fig. 4. The effect of intraperitoneal administration of fluoxetine on the mean spike frequency of penicillin-induced epileptiform activity. Five or 10 mg/kg (i.p.) fluoxetine significantly reduced the mean frequency of epileptiform activity 40 and 50 min after administration. A high fluoxetine dose (20 mg/kg i.p.) significantly increased mean frequency of epileptiform activity 40 min after fluoxetine administration (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). The frequency of epileptiform ECoG activity (%) depends on the frequency of epileptiform ECoG activity before and after the drug administration. Thus, it is calculated using the formula; Frequency (%) = mean spike frequency after drug administration / mean spike frequency before drug administration × 100.

5 mg/kg fluoxetine groups, respectively. The 5 mg/kg fluoxetine injection decreased mean frequency by 58% ($p < 0.05$) and mean amplitude by 60% ($p < 0.01$) in ECoG activity compared with the control group (Figs. 3B/C, 4, and 5).

Intraperitoneal administering of 10 mg/kg fluoxetine significantly decreased mean frequency and amplitude of epileptiform activity 50 and 120 min after the administration, respectively. As shown in Tables 1 and 2, mean frequency and amplitude in ECoG were 49 ± 3 and 31 ± 4 spike/min and 823 ± 58 and 620 ± 35 μV in control group (penicillin, 500 IU) and 10 mg/kg fluoxetine group, respectively. Fluoxetine injection of 10 mg/kg decreased mean frequency by 69% ($p < 0.01$) and mean amplitude by 73% ($p < 0.05$) in ECoG activity compared with control group (Figs. 3B/D, 4, and 5).

Intraperitoneal fluoxetine at a dose of 20 mg/kg significantly increased the mean frequency and amplitude of epileptiform activity 40 and 120 min after fluoxetine administration. As shown in Tables 1 and 2, the mean frequency and amplitude in ECoG were 46 ± 3 and 63 ± 9 spike/min and 823 ± 58 and 1089 ± 63 μV in control (penicillin, 500 IU) and 20 mg/kg fluoxetine group, respectively. Fluoxetine injection of 20 mg/kg increased mean frequency by 147% ($p < 0.01$) and mean amplitude by 123% ($p < 0.05$) in ECoG activity compared with control group (Figs. 3B/E, 4, and 5).

Low and moderate fluoxetine doses (5 and 10 mg/kg) decreased penicillin-induced epileptiform activity while the highest dose (20 mg/kg) increased it.

4. Discussion

The most frequent comorbid psychiatric problem in patients with epilepsy is depression [33]. Fluoxetine is a widely used SSRI antidepressant drug. Many studies revealed the effects of fluoxetine on seizures in different epilepsy models [25–28]. To our knowledge, the present study is the first to examine the effects of fluoxetine on the penicillin-induced seizure in rats, a model for simple partial epilepsy. The results of the study showed that low (5 mg/kg) and moderate (10 mg/kg) fluoxetine doses decreased epileptiform activity in penicillin-induced seizure model. On the other hand, higher dose of fluoxetine (20 mg/kg) increased epileptiform activity effect in this model.

Anticonvulsant and proconvulsant effects of fluoxetine have been reported in clinical and experimental studies. Three clinical studies with fluoxetine have suggested possible antiepileptic effects [18,19,30]. Favale et al. [18] carried out a clinical study on 17 patients with focal epilepsy, who were monitored for an average of 14 months, and reported prevention of seizures in six patients and decreased seizure frequencies by 30% in the remaining 11 patients. Meador [19] found that fluoxetine reduced seizures in an adult woman with Dravet syndrome. Thomé-Souza et al. [34] reported that fluoxetine treatment was effective in eliminating depression and providing effective seizure control in eight children and adolescent patients with depression and epilepsy. In addition, several experimental studies showed that fluoxetine was effective against audiogenic seizures in mice and rats [22,23], maximal electroshock-induced epileptiform activity in rats [24], and

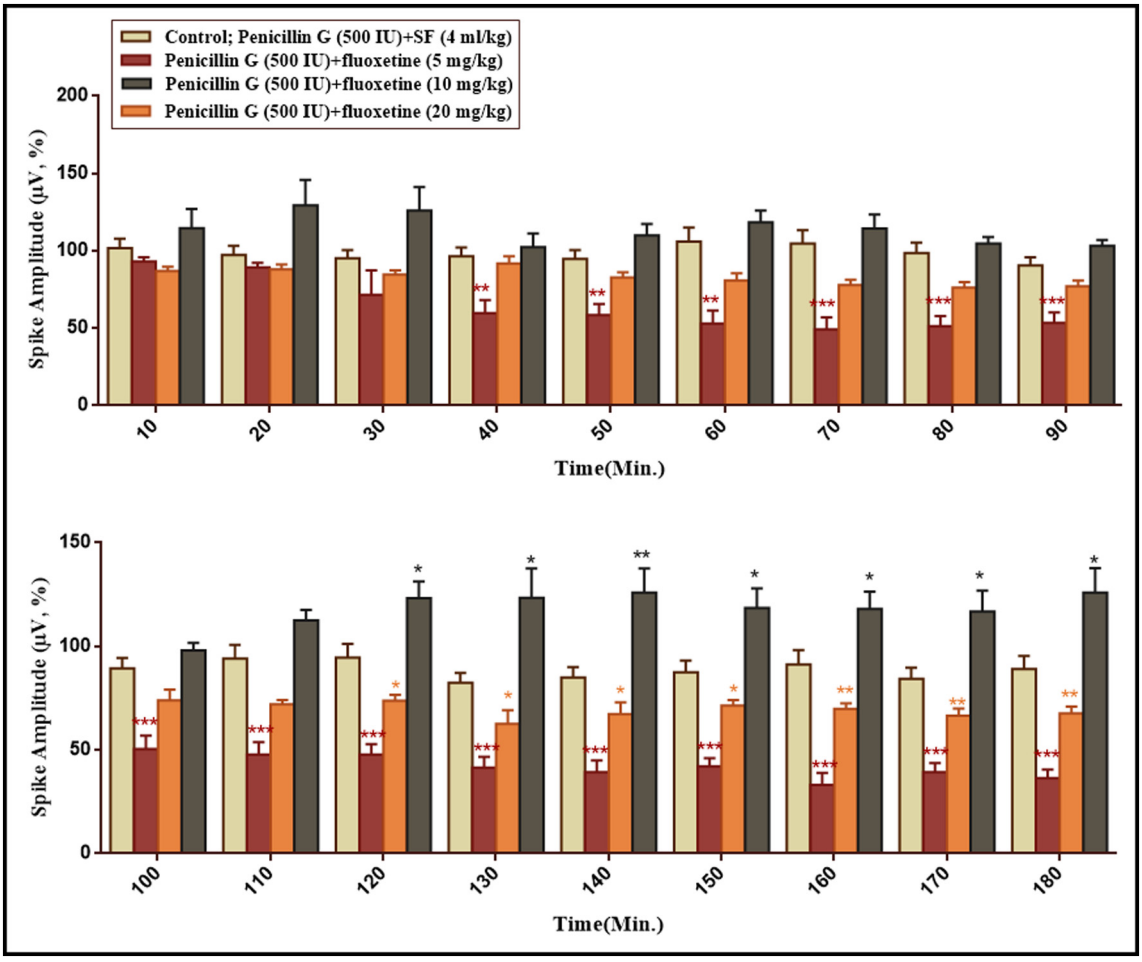

Fig. 5. The effects of intraperitoneal fluoxetine administration on spike amplitude in penicillin-induced epileptiform activity. Five or 10 mg/kg (i.p.) fluoxetine significantly reduced the mean spike amplitude of epileptiform activity 40 and 120 min after administration. Twenty milligrams/kilogram (i.p.) fluoxetine dose significantly increased mean spike amplitude of the epileptiform activity 120 min after the administration (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). The percent amplitude of epileptiform ECoG activity value depends on the amplitude of the epileptiform ECoG activity before and after the drug administration. Thus, it is calculated using the formula: Frequency (%) = mean spike amplitude after drug administration / mean spike amplitude before drug administration × 100.

focally evoked limbic motor seizures in rats [20]. As an anticonvulsant, fluoxetine (5 mg/kg) exerted a protective effect in limbic motor seizure model [20]. Shiha et al. [25] demonstrated that acute treatment with 10 mg/kg fluoxetine considerably increased the seizure latency time in 4AP-induced epileptiform activity. In the present study, fluoxetine (5 or 10 mg/kg, i.p.) significantly decreased mean spike frequency and amplitude of the epileptiform activity. Our results are in accordance with previous studies, which showed the anticonvulsant effect of fluoxetine in other epilepsy models.

As a possible mechanism for low- and medium-dose decreased epileptiform activity effect of fluoxetine, Shiha et al. [35] demonstrated that subacute fluoxetine administration (10 mg/kg) increased the density of GABAA receptor in the dentate gyrus and CA1–CA2 regions in a pilocarpine-induced rat seizure model. Penicillin leads to GABA inhibition in the cortex and increases the secretion of glutamate from cortex slices, thereby causing epileptic seizures [36]. Increased GABA activity by low and moderate doses of fluoxetine may decrease spike frequency and amplitude in penicillin-induced epileptiform activity. Many studies demonstrated that fluoxetine has a direct off-target effect on voltage-gated Na(+) and T-, N-, and L-type voltage-gated calcium channels, and this effect is inhibitory [37,38]. It has been found that increased neuronal activity during epilepsy could be associated with voltage-gated Na+ and Ca2+ channels [39,40]. Besides, conventional anticonvulsant drugs are known to inhibit voltage-dependent Na+ and Ca2+ channels [41–45]. It was reported that the extracellular Ca2+ level increases before the onset of penicillin epilepsy in anesthetized cats, and it was found that penicillin could cause bursts by acting on parasynaptic routes and Ca2+ [46]. The abovementioned results support the assumption that the anticonvulsant action of fluoxetine is due to its inhibition of Ca2+ and Na+ channels.

There are studies in the literature showing that fluoxetine has a proconvulsant effect. Clinical studies reported that fluoxetine induced seizures in a person with Down syndrome [17]. Chronic fluoxetine treatment (10 mg/kg) significantly increased the duration of seizures in kindling epileptic rats [28]. Ferrero et al. [47] demonstrated that chronic fluoxetine administration lowered seizure threshold. In pilocarpine-induced status epilepticus rats, fluoxetine (10 and 20 mg/kg) shortened the latency to first seizure and increased mortality rate and proconvulsant effect in a dose-related fashion [27]. Fluoxetine is generally used as 20–60 mg day/l in the treatment of patients with depression [48]. However, this study showed that 20 mg/kg dose of fluoxetine increased the spike frequency and amplitude in penicillin-induced epileptiform activity.

A possible explanation for the high-dose increased epileptiform activity effect of fluoxetine could be derived from a study by Sung et al. [49] reporting that fluoxetine inhibits Kv3.1 channels in a dose-dependent manner. Low doses of fluoxetine do not inhibit Kv3.1 channels. However, higher fluoxetine doses inhibit most of these channels [49]. Kv3.1 channels and voltage-gated K+ channels are involved in the generation of fast and repetitive spikes [50,51]. They are highly

expressed in GABAergic inhibitory neurons [52–54]. The expression of the Kv3.1 channels in interneurons suggests that a lower Kv3.1 current will increase the net excitability of neural networks by reducing the inhibitory neuron activity. Thus, inhibition of Kv3.1 channel by a high dose of fluoxetine may elevate epileptic activity of the neural networks by interfering with the repetitive firing of inhibitory neurons.

Gall et al. [55] demonstrated that fluoxetine reduced the duration of seizure-like events considerably while increasing the frequency of the seizure-like events in a low-Mg model of epilepsy. A lot of studies demonstrated that the activating voltage-gated sodium channels are of the principal responsibility for the depolarizing phase of the action potential and neuronal excitation. Increased abnormal neuronal excitation causes epileptiform activity. Similar to K + channels, the explanation for the increased epileptiform activity action of fluoxetine might be related to the idea that fluoxetine inhibits slow inactivation process of voltage-gated sodium channels in a use-dependent manner [55,56]. This may be responsible for inducing repetitive firing and increasing neuronal activity [57]. A previous study indicated that imipramine (antidepressant drug) is proconvulsant in high doses and anticonvulsant in low doses [58]. Another antidepressant drug study demonstrated that lower and moderate duloxetine (selective inhibitor of serotonin and norepinephrine reuptake) treatment decreased seizure activity but higher duloxetine treatment rates influence epilepsy onset and a risk factor for the development of seizures in PTZ-induced rat [59]. A study demonstrated that citalopram decreased seizure susceptibility at low rates while increasing it at higher rates in PTZ-induced clonic seizure model [60]. This type of combined, decreased epileptiform activity and increased epileptiform activity was observed in this study.

Also, SSRI antidepressant treatment could block the serotonin transporter (SERT) [61] and lead to prolonged activation of postsynaptic 5-HT receptors and elevated synaptic serotonin level, which in turn could produce the 5-HT syndrome. Thus, neuromuscular excitation is altered, and seizures develop [62,63]. This theory might explain the decreased epileptiform activity action of low and medium dose fluoxetine and increased epileptiform activity effect of high dose fluoxetine in the present study.

5. Conclusion

In the present study, administration of low to moderate fluoxetine doses alleviated the seizures and provided an anticonvulsant effect on penicillin-induced epileptiform activity in rats. However, a higher dose of fluoxetine seems to have the proconvulsant effect, aggravating the epileptiform activity. Even though the results are based on animal studies (rats), a low and moderate dose of fluoxetine treatment appears to be safe in terms of posing risk for epileptiform activity and could be recommended for the treatment of patients with simple partial epilepsy. However, high doses of fluoxetine should be avoided in these patients.

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None.

Declaration of interests

None.

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