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The role of dopamine D2-like receptors in the occurrence of LFS effects on spontaneous synaptic currents

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ABSTRACT

Introduction: Low-frequency electrical stimulation (LFS) has been considered as a new treatment method for epilepsy patients resistant to drug treatment, but its mechanism of action is not fully understood. Gi protein-coupled receptors such as dopamine D2-like receptors may play a role in mediating the effects of LFS. In this study, the role of dopamine D2-like receptors in the effects of LFS on seizure-induced spontaneous synaptic activity in the hippocampal CA1 region of fully kindled rats has been investigated.

Methods: Animals were kindled by semi-rapid kindling method (6 stimulations per day) by electrical stimulation of the hippocampal CA1 region. In LFS-treated groups, animals received 4 LFS packets at 5 minutes, 6 hours, 24 hours, and 30 hours after the last LFS stimulation. Each LFS package consisted of 4 series with an interval of 5 minutes, and each series consisted of 200 pulses, and the pulse duration was 0.1 ms with a frequency of 1 Hz. Haloperidol (D2 receptor antagonist, 2µm) or bromocriptine (D2 receptor agonist, 2µg/µlit) was injected into the lateral ventricle immediately after the last kindling stimulation, before applying LFS.

Results: The obtained results showed that the application of LFS in kindled animals did not affect the spontaneous excitatory currents in the hippocampus, but it caused a decrease in the spontaneous inhibitory currents in the hippocampus. D2 receptor agonist did not mimic the effects of LFS. The use of haloperidol as an antagonist of dopamine D2 receptors did not affect the effects of LFS.

Conclusion: It may be suggested that spontaneous excitatory and inhibitory potentials are not a suitable quantity to investigate the effectiveness of LFS.

Keywords: seizures, low-frequency stimulation; dopamine D2 receptors; synaptic transmission

INTRODUCTION

Epilepsy is one of the most common neurological diseases in the world, which affects about 1-2% of people (1). A seizure is a transient occurrence of symptoms or signs caused by abnormal, excessive and coordinated activity of neurons in the brain. Despite existing a lot of anti-epileptic drugs, approximately 20 to 30 percent of epilepsy patients are resistant to drug treatments (2), and many of them cannot undergo surgery due to the lack of identification of the seizure center (3). Therefore, it seems necessary to find new treatment strategies that can be effective in reducing convulsions. In the last two decades, deep brain electrical stimulation, as an auxiliary treatment and sometimes as the main treatment method, has been considered in treatment-resistant epilepsy patients, and one of the most important patterns used in this method is electrical stimulation with low frequency (LFS) (4). It has been observed that in patients with temporal lobe epilepsy, LFS reduces the number of spikes

between attacks (5-7). In addition, the application of LFS (usually 1 to 3 Hz) reduces the intensity of seizures caused in various laboratory models, including kindling (7).

One of the most important areas that plays a role in spreading seizure waves to other brain areas is the CA1 area of the hippocampus (8). The hippocampus plays an important role in the formation of long-term memory in humans (9) and spatial memory in rodents (10, 11). Severe damage to this area has been seen in temporal lobe epilepsy in humans and rats. On the other hand, impairment of synaptic strengthening in the hippocampal CA1 region (12-15) and impairment of learning and spatial memory following kindling (16, 17) have been shown in previous studies. It is possible that the disruption of synaptic transmission caused by kindling is involved in seizure severity and propagation (18, 19).

Despite the existence of much evidences about the anticonvulsant effects of LFS, the mechanisms through which LFS exerts its anticonvulsant effects have not yet been fully elucidated. In several studies, the role of neurotransmitters whose receptors are coupled with inhibitory G protein (Gi), such as galanin (20), adenosine (A1 receptor) (21), serotonin (22) and endocannabinoids (CB1 receptor) (23) as Mediating factors of antiepileptic effects of LFS has been mentioned. Dopamine is one of the important neurotransmitters in the central nervous system, whose D2-like receptor couples with inhibitory G protein (G_i). Laboratory and clinical evidence show that dopamine has anticonvulsant effects through the D2-like receptor (24, 25). Also, the dopamine D2-like receptor signaling pathway leads to a decrease in neuronal excitability, neuronal protection and synaptic weakening (26). Therefore, the aim of this study is to investigate the mediation role of dopamine D2-like receptors in the recovery effects of LFS on kindling-induced disorders in memory and learning and synaptic strengthening in completely kindled animals.

MATERIALS AND METHODS

Animals

In this research, male Wistar rats were used in the age range of 8-9 weeks and weight range of 270-290 grams at the beginning of the experiments. The animals were kept at a temperature of 22 ± 2 ^{o}C and a light cycle of 12 hours of light/12 hours of darkness in the animal house of the Department of Physiology of Tarbiat Modares University and had free access to water and food during the experiment. All the experiments were carried out in compliance with the ethical principles of working with laboratory animals as determined by the Medical Ethics Committee of the Faculty of Medical Sciences of Tarbiat Modares University. In order to minimize the effect of circadian rhythms on the experimental data, the experiments were always performed at a certain time of the day.

Chemicals

In this research, the drug haloperidol (purchased from Sigma) was used as an antagonist of D2-like dopamine receptors, and the drug bromocriptine (purchased from Tocris) was used as an agonist of D2-like dopamine receptors. Haloperidol (2 µM) was dissolved in 10 ml of 90% ethanol. Then the prepared solution was diluted with artificial cerebrospinal fluid (ACSF). Bromocriptine (2 µg/µlit) was dissolved in a certain volume of 90% ethanol, then the desired dose was obtained by diluting the solution with ACSF.

Animal surgery

Animals were anesthetized by intraperitoneal injection of a mixture of 10% ketamine (Alfasan, The Netherlands) and 2% xylazine (Alfasan, The Netherlands) (100 and 10 mg/kg, respectively) and then rats were placed in the stereotaxic instrument in such a way that their skulls were in a horizontal position. A longitudinal incision was made along the middle sagittal groove in the scalp and the surface of the skull was cleaned by alcohol to determine the bregma point. The position of Shaffer's path in the right hemisphere to place the stimulating electrode in relation to bregma was determined using the Paxinos and Watson atlas (in mm: AP=-1.3, L=1.3 and V=2 to 3.5 below dura). Also, the position of the radiatum layer of the CA1 region for placing the recording electrode was determined (in mm: AP=2.8, L=1.8 and V=2.3 to 2.5 below dura) (27).

The electrodes and screws were fixed on the animal's skull with dental cement and the pins connected to the electrodes were put in a socket and the socket was fixed on the surface of the skull with dental cement. Animals were rested for 10 days in order to heal the wounds and be trained.

Application of kindling stimulation

A semi-fast kindling method was used to stimulate the animal. First, the afterdischarge (AD) threshold was determined for each animal. The Shafer pathways were stimulated by a current of 30 µA. If ADs were recorded (for at least 10 seconds), this current intensity was known as the threshold intensity. Otherwise, within 10 min intervals, the intensity of the current was gradually increased by 10 µA until intensity threshold was reached. In this method, the animals were stimulated with a monophasic square wave with a frequency of 50 Hz, a pulse duration of 1 ms and a duration of 2 s. These daily stimulations were applied to the animal in the form of 6 stimulation packages at an interval of 20 min, and the stimulations continued until the animal was kindled and showed stage 5 seizures for 3 consecutive days.

Drug injection

To inject the drug into the lateral ventricle, a PE-20 polyethylene tube connected to a G 30 needle was used. The drugs were injected by a syringe pump at 2 µl/min in a period of two min.

Low frequency electrical stimulation (LFS)

To apply LFS, 4 packets of 200 pulses with a frequency of 1 Hz and a pulse duration of 0.1 ms at the test pulse intensity were used for each animal. Stimulations are applied on two consecutive days, twice a day, with an interval of 6 hours. LFS was applied in the respective groups, 5 min after the last kindling stimulation, and in the groups that received only LFS at the same time as the kindled groups.

Preparation of tissue sections from the hippocampus

48 hours after the last kindling stimulation, the animals were anesthetized with CO_2 and their heads were removed. Then the brain was quickly taken out and placed in a cold cutting solution (with a temperature of 0 to 4 degrees Celsius). The composition of the cutting solution (in mM) included KCl 2.5, $CaCl_2$ 0.5, $MgCl_2$ 2, $NaHPO_4$ 1, $NaHCO_3$ 2.26, sucrose 238, and D-glucose 11, which was continuously bubbled with carbogen gas (containing 95% O_2 and 5% CO_2). The osmolarity of this solution was in the range of 294 to 300 milliosmoles and its pH was set at 7.4 ± 0.3. Transverse sections with a thickness of 400 µm were prepared by the VT1200S Vibroslicer. The prepared slices were transferred to a container containing artificial cerebrospinal fluid (ACSF) and incubated for 1 hour at 35°C. ACSF composition (in mM) consisted of NaCl 127, KCl 2.5, $NaHPO_4$ 1, $NaHCO_3$ 25, $CaCl_2$ 2, $MgCl_2$ 2 and D-glucose 10 continuously perfused with carbogen gas. The osmolality of this solution was in the range of 294 to 300 milliosmoles and its pH was adjusted to 7.4±0.3 using NAOH. Then, the slices were transferred to room temperature (23 to 25 degrees Celsius) and kept at this temperature until the end of the experiment.

Whole cell recording

To record brain slices, an immersion type recording chamber was used, which was fed with ASCF at a rate of 1.5 to 2.5 ml per minute. Recordings were done at room temperature. After transferring each of the slices to the recording chamber, a small mesh screen was placed on them to prevent the movement of the slices during recording.

Recordings were made from the cell bodies of pyramidal neurons in the CA1 region of the hippocampus. To observe the neurons, we used a microscope with a fixed platform (AXIOSKOP 2 FS MOT, CARL ZEISS, Germany) equipped with an infrared camera (IR CCD CAMERA, model IR-1000, MTI, USA) and a water-immersed objective lens with a magnification of 40× was used. To prepare recording microelectrodes, filament glass micropipettes with borosilicate material (outer diameter 1.5 mm, model GC150-11, HARVARD APPARATUS, England) were used, which were pulled using a horizontal electrode puller (model P-97, SUTTER company). The resistance of the electrodes after being filled with intracellular solution and placing their tips in ACSF was between 4 and 6 megaohms.

Cells with access resistance (RA) less than 25 megohms were recorded. In addition, RA was checked during the experiment and if its changes were more than 20% during the experiment, the data from that cell was removed and not analyzed. Recording was done in whole cell configuration at low -pass filter of 2 kHz and a sampling rate of 10 kHz by an amplifier device (model MULTICLAMP 700B, Molecular Devices, USA) equipped with an analog-to-digital converter system (model DIGIDATA 1440, Molecular Devices, USA) and then transferred to the computer and recorded using pCLAMP version 10.

The recording of synaptic currents related to glutamate AMPA and NMDA receptors and synaptic currents related to GABA receptors was performed in voltage clamp mode. It was necessary to inhibit the inhibitory currents while recording the excitatory currents and vice versa to inhibit the excitatory currents while recording the inhibitory currents electrophysiologically. For this purpose, the reverse potential of the excitatory and inhibitory currents in the composition of the intracellular solution used was calculated. The reverse potential for glutamate currents was +25 mV and for GABAA receptors was -45 mV. In all groups, excitatory currents (AMPA, NMDA) were recorded by clamping the membrane at the reverse potential of GABAA (-45 mV) and inhibitory currents were recorded by clamping the membrane at the reverse potential of glutamate (+25 mV).

The intracellular fluid used to record synaptic evoked currents caused by glutamate receptors and GABA receptors in CA1 pyramidal neurons contained the following compounds in mM: $CsMeSO_4$ 102, HEPES 20, TEA-Cl 5, BAPTA 11, EGTA 0.2, MgATP 2, NaGTP 0.3 and QX-314 5. The pH was set in the range of 7.25 to 7.30 and the osmolality was set in the range of 285 to 290 milliosmoles. The pH of intracellular fluid was adjusted using CsOH.

To record the evoked and spontaneous postsynaptic excitatory currents, the membrane holding potential was set to -45 mV and the spontaneous excitatory postsynaptic currents were recorded for 5 minutes. To record the inhibitory currents, the membrane potential was clamped at +25 mV and the spontaneous inhibitory currents were recorded for 5 minutes.

Experimental groups

Animals were randomly divided into 6 groups: 1. Control group: This group had two subgroups. In the first subgroup, animals were operated and after the end of the recovery period, they were given time for 12 days (10 days average time required for kindling and reaching the fully kindled stage and 2 days equivalent time to receive LFS) and on the twelfth day Intracellular recording was performed from animals (n=3). In the second subgroup, the animals were not operated, but when they reached the age of the first subgroup on the last day of the experiment, they were prepared for intracellular recording (n=3). Since no significant difference was observed in any of the parameters recorded in the intracellular recording method between the animals of the first subgroup and the second subgroup of the control group, the data of these subgroups were merged together and considered as a single control group. 2. Kindled group: In this group, after the recovery period, the animals received kindling stimulations until they were completely kindled, and 48 hours after the last kindling stimulations, intracellular recording was performed. 3. Kindled +LFS group: In this group, similar to the Kindle group, the animals received kindling stimulations daily to reach the complete kindling stage, but in this group, 5 minutes after the end of the last kindling stimulations, LFS was applied to the animal with the mentioned specifications. And 12 hours after the last LFS stimulation, intracellular recording was done. 4. LFS group: In order to investigate the effect of LFS stimulation alone on intracellular excitatory and inhibitory currents, 10 days after the end of the recovery period (the average number of days required for kindling and reaching the completely kindled stage), LFS stimulation with the said protocol, with an intensity of 200 microamps (equal to the average intensity of the test pulse in Kindled and Kindled + LFS groups) was applied and intracellular recording was done 12 hours after the last LFS stimulation. 5. Kindled + LFS + Haloperidol group: The process of conducting experiments in this group was similar to the Kindle + LFS group, with the difference that

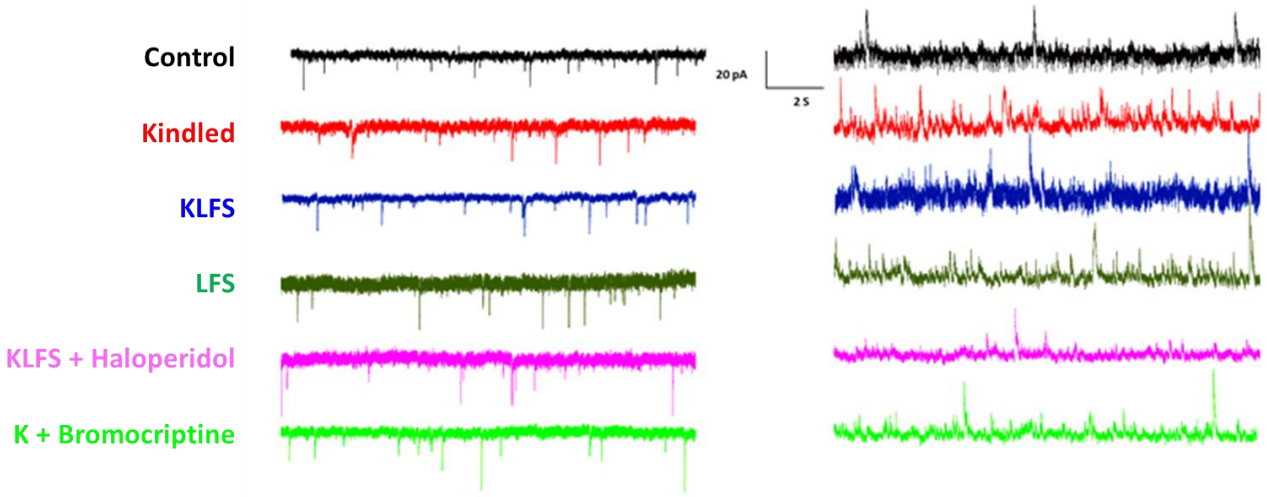

Figure 1. Comparison of spontaneous excitatory and inhibitory currents in experimental groups. Figure shows a sample recording of spontaneous excitatory and inhibitory currents

before each LFS application, the D2-like receptor antagonist haloperidol (2 µmol) was injected ICV with a volume of 1 microliter. 6. Kindled + bromocriptine group: the process of conducting experiments in this group was similar to the Kindled + LFS group, with the difference that instead of each LFS stimulation, the animals received dopamine D2-like receptor agonist (bromocriptine) 2 µg/µlit as ICV with a volume of 1 microliter.

Statistical analysis

Statistical analysis of data was done using Prism software version 6.01 (GraphPad Software Company, USA) in Windows environment. The data are presented as (mean ± standard error of the mean) and $p<0.05$ was considered as the minimum level of significance. A one-way analysis of variance test was used to compare the parameters of intracellular recordings.

RESULTS

In order to investigate the role of dopamine D2-like receptors in the occurrence of LFS effects on spontaneous synaptic currents in Kindle animals, the amplitude, slope and the interval between excitatory and inhibitory events were analyzed. In the data analysis, using one-way analysis of variance with Tukey's post hoc test, no significant difference was observed between the experimental groups in amplitude, slope and distance between the occurrence of spontaneous excitatory and inhibitory currents (Figs 1 and 2).

DISCUSSION

The results of the present study showed that the application of LFS at a pattern that had anticonvulsant action, had no effect on spontaneous excitatory and inhibitory post synaptic currents in the CA1 pyramidal neurons of the hippocampus.

For various reasons, the kindling model is considered a suitable laboratory model for studying temporal lobe epilepsy. In this model, it is possible to control a wide range of important variables, such as seizure center (stimulated area), seizure intensity, frequency and time of seizures, as well as the interval between seizures and the possibility of conducting behavioral tests. There are also outstanding similarities between kindling and temporal lobe epilepsy-like, the similarity of behavioral patterns and electrogram in kindling and epileptic patients and similar response to anticonvulsant drugs and the occurrence of spontaneous attacks after high stimulation and also the creation of permanent changes in brain function following the completion of kindling, this model is considered It is clinically comparable to temporal lobe epilepsy (28, 29).

In this study, a model of LFS was used, whose anticonvulsant and antiepileptic effects were previously shown in our laboratory. Applying LFS with this pattern reduces the intensity of

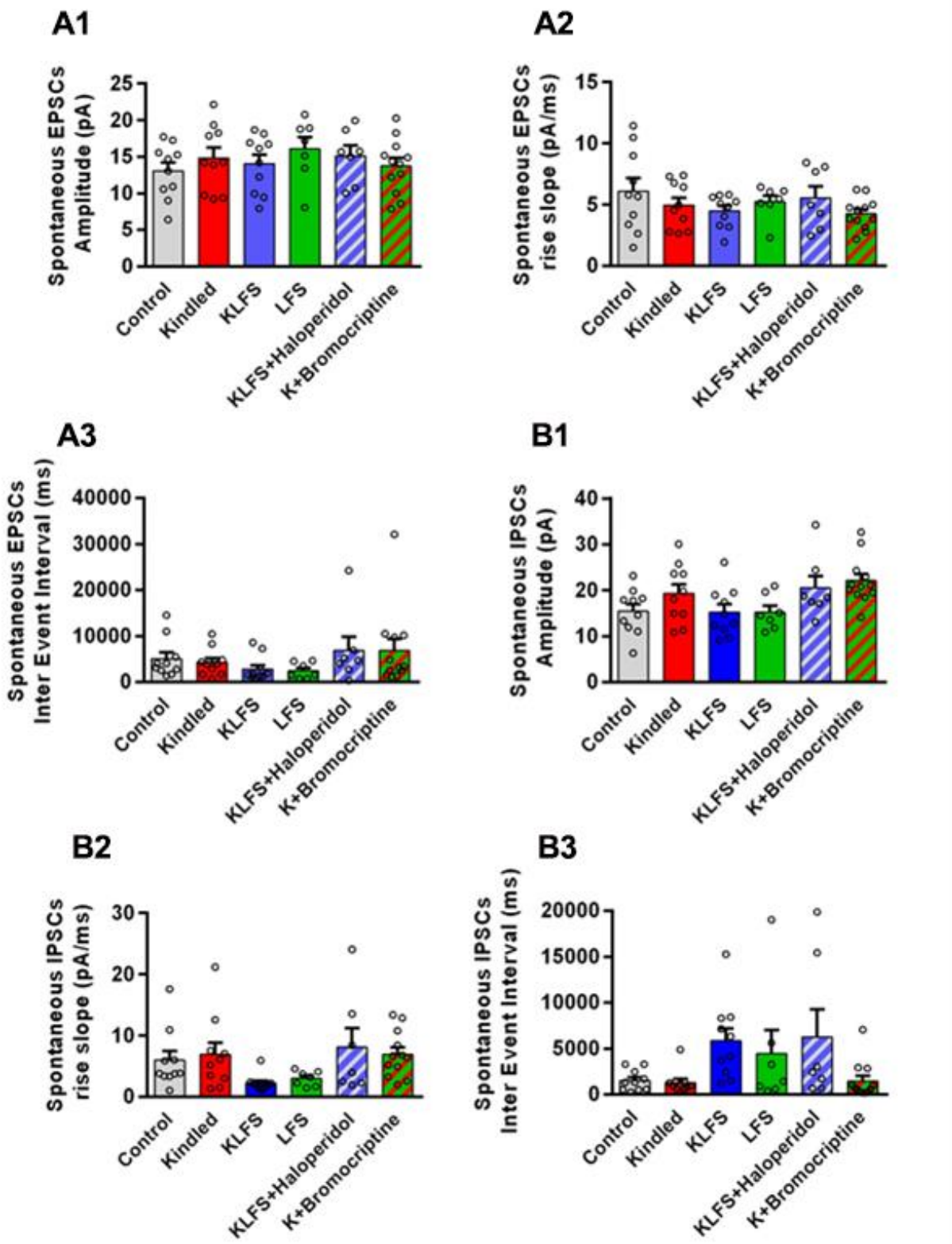

Figure 2. Comparison of spontaneous excitatory and inhibitory currents in experimental groups. In A1, A2 and A3, the amplitude, slope and interevent intervals are compared between spontaneous excitation events, no significant difference was observed between the experimental groups. In B1, B2 and B3, the amplitude, slope and interevent intervals are compared among experimental groups. There was no significant difference between the experimental groups in the interval between inhibition events. Data are mean±SEM. In Control, Kindled and KLFS groups: n=10. In LFS and KLFS+ Hallparidol groups: n=7, in K+Bromocriptine group: n=12.

seizures, the duration of subsequent discharge waves and prevents the acquisition of epilepsy during the kindling process (30-34). Also, anticonvulsant and antiepileptic effects of LFS (1 Hz) have been reported in other studies in Kindled animals and in models of acute seizures induced in brain slices (35-37).

The hippocampus is an important structure in the temporal lobe that is both affected by seizures and has an effect on seizures. Anatomical studies have shown that significant morphological changes occur in the hippocampus in temporal lobe epilepsy. The most common changes include the loss of neurons in the dentate gyrus and pyramidal layer CA1 and CA3, sprouting of mossy fibers and hippocampal sclerosis (38). Several clinical studies have also reported that hippocampus stimulation in patients with temporal lobe epilepsy has significant improvement results on the recurrence of seizures in patients and even in a number of patients it has resulted in complete relief from seizures (39-41).

Despite the evidence that low-frequency electrical stimulation is effective in controlling seizures and ameliorating cognitive impairment and no tissue damage has been reported following the application of LFS (42), currently it can be considered not as an alternative treatment but as a complementary treatment. The reasons for this, are the unknown mechanisms of LFS action and its side effects, the lack of sufficient clinical evidences, and the difference in the obtained results according to brain regions and electrographic parameters. Therefore, studies on the search for optimal stimulation parameters and stimulation area, as well as finding the effect mechanisms and unwanted side effects of this treatment method are very necessary for the management of clinical convulsions.

In the evaluation of spontaneous excitatory and inhibitory post-synaptic currents, there was no difference between different groups in the indicators of amplitude, slope and interval between events (inter event interval). The lack of difference in the amplitude and slope indices was reported in the previous study of our laboratory. But regarding the interval between events, our finding is contrary to the previous report, which showed that kindling decreases the IEI of spontaneous excitatory postsynaptic currents and increases the IEI of spontaneous inhibitory postsynaptic currents, and applying LFS prevents these changes (32) that the observed difference may be related to the difference in recording time that was mentioned earlier.

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DECLARATIONS

Authors have no conflict of interest to declare.

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