

Acoustic Range Electric-Magnetic Field Exposure Decreases Cortical Excitability in Genetically Epilepsy-Prone Rats

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Abstract

In the present study, we examined the effect of acoustic range of electric-magnetic field (EMF) on the behavioral manifestation of seizure in genetically epilepsy-prone rats (GEPRs) of Krushinsky-Molodkina strain. A 5-days exposure to EMF (10000 -15000 Hz frequency, 1.5 m/Tesla, during 20 min) resulted in partial or complete suppression of behavior seizure activity in GEPRs. Besides, on the background of EMF the latency period of first wild run was increased. On the same conditions, duration of wild run decreased.

Audiogenic stimuli obtained in GEPRs changed the ECoG activity of somatomotor cortex only in audiogenically-kindled animals. Findings of this study suggest that the regulation of the behavioral manifestation of seizure in GEPRs does not involve the cortex; it is mainly regulated by brainstem structures. We concluded that acoustic range of EMF could apply for suppression of behavioral manifestation of seizure. Audiogenic stimuli obtained in GEPRs changed the ECoG activity of somatomotor cortex only in audiogenically-kindled animals. Findings of this study suggest that the regulation of the behavioral manifestation of seizure in GEPRs does not involve the cortex; it is mainly regulated by brainstem structures. Rostral part of cortex has significant role in manifestation of seizure activity in audiogenically kindling GEPRs. We concluded that acoustic range of EMF could apply for suppression of behavioral manifestation of seizure.

Keywords: Electric-Magnetic Field; Seizure; Rats; ECoG

Introduction

Epilepsy is one of the most common disorders. According to the WHO (World Health Organization) fact sheet, epilepsy affects about 50 million people of all ages worldwide. Despite the fact that it is possible to treat epilepsy using pharmacological substances, about 30-40% of the patients are resistant to such treatment (WHO, Media Center 2016). In addition, a long-term consumption of the drugs negatively affects the patients' cognitive functions [1-3]. The effectiveness of pharmacological agents, used for epilepsy treatment is

limited due to incomplete understanding of the mechanisms involved in the pathogenesis of the disease. Therefore, a goal of modern psychiatric research is to find the new ways for anti epilepsy therapy, which will give the opportunity to cure this group of patients.

The EMF exposure is a noninvasive treatment method; it is used as a complementary to the drugs, for treating different neurodegenerative diseases (Parkinson's disease, schizophrenia, depression, tinnitus, etc.) [4,5]. EMF exposure can also be used as a separate treatment therapy [6]. Furthermore, repetitive TMS Transcranial

Magnetic Stimulation) is seen as a safe treatment method, without enduring side effects: no long-term neurological, cognitive, or cardiovascular side effects are reported.

The EMF appears to be biologically active, penetrating into the living tissue without any impediments [7,6]. However, it is unclear how the low-frequency EMF can block seizure activity.

One of the basic provisions underlying the given research is the assumption that the macromolecules which constitute the living organism are subjected to the conformational fluctuations under the conditions of EMF impact. In our opinion the artificially created EMF may change the tonic activity of the cells located in the local area of its action and because of it the mode of neural impulses formation. Because of it, the tonic activity is also changed in the central nuclei, through which the various sensory afferent ways coming from the various parts of the body are passing. On the other hand, oscillations of acoustic range (which belong to low frequency oscillations) due to their activity can cause the intensification of chemical processes. Then, oscillations of this range can be used both for process stimulation, intensification and optimization and for their attenuation. It will depend on impact mode and selection of duration. Both a change in membrane ion channel permeability and oriented redistribution of radicals, liquid-crystalline macromolecular structures, metalloproteins (hemoglobin, vitamins) and molecular water fragments may occur under influence of low frequency magnetic fields [8,9].

The goal of this study was to explore the potential mechanisms underlying the impact of EMF exposure on the epilepsy. In GEPRs and inbred white rats, we examined the effect of EMF exposure on ECoG activity in sensomotoral cortex. We attempted identify the optimal parameters of repeated EMF exposure, which fully or partially depress the ECoG and behavioral seizure manifestations.

Methods

Subjects and Surgical Procedures

Experiments were conducted on male white, inbred rats and GEP of Krushinsky-Molodkina (KM) strain rats (n=14). This strain of rats manifests short lasting seizure activity in neonatal age and fully-fledged seizure activity after hierarchical implication of brainstem structures [10]. In response to a strong sound (the bell -90-dB, during 60 sec), GEPRs display either fear reaction accompanied by facial muscle clonus (group a) or fear reactions with elevated motor act responses (wild running, jumps), which are accompanied with tonic-clonic

behavioral seizures (group b). The present study was conducted on animals of group b.

Under ketamine (5-10 mg/kg intraperitoneally) anesthesia, the rats were implanted with stainless bipolar electrodes (8IE3633SPCXE ELEC 0.05-125 MM SS Plastics One) into sensomotoral area of neocortex.

Experimental Paradigm

At the beginning of experiments, both control (Inbred, white male rats n=7) and experimental (GEPRs n=14) rats were placed into coil for EMF exposure with defined parameters of magnetic field (see below) for a 20-min session. 10 min after the session of EMF exposure, the animals were re-tested. The GEPRs (with or without exposure) were given audiogenic stimuli, for 60 secs, before and after testing in open field for monitoring behavior correlates of seizure activity.

EMF Exposure

For EMF exposure (carried for five consecutive days), we used the coil designed at Tbilisi Technical University, Georgia. Parameters of magnetic field (stimulus frequency, its intensity and train duration), which partially or fully depressed ECoG and behavior manifestation of seizure activity, were established during pilot experiments. For repetitive (a 5-days) EMF exposure, we used the following parameters: (10000-15000 Hz, 1-1.5 m/Tesla).

EEG Registration

ECoG activity of seizure was registered before, during and after EMF exposure in free movement rats.

The Open Field Test

Emotional-motivational status of the rats was tested in a chamber of 80 cm in diameter surrounded by 30 cm height walls, Open Field. The floor of the chamber was divided into 32 squares and lighted with 200 W lamp. The rats were video-recorded for initial 5 minutes after the placement into the Open Field, for three consecutive days (the same time of day). We registered the following parameters: entering the center, numbers of crossed squares, head raise, vertical stands, the frequency and duration of grooming, number of fecal boluses and urination. After each trial, the chamber was cleaned with 30 % ethanol solution.

Data Analysis

We determined the parameters of locomotor and emotional-motivated activity in Open field (see above),

the parameters of behavioral (latency of the first wild run, duration of the first wild run, duration of pause, and duration of second wild run, duration of tonic-clonic seizure and of post-ictal activity) and ECoG seizure activity were determined as well.

Statistics

Data obtained were processed using adequate statistical program. Data reliability was assessed using parametric and non-parametric techniques, with the use of one- and two-way layout of factorial analysis.

Results and Discussion

The Effect of EMF Exposure on Behavior Manifestation of Seizure Activity in GEPRs

During experiments revealed two subgroups of GEPRs. In the first group of animals, audiogenic stimuli resulted

in wild running (right after the delivery of stimuli) followed by tonic-clonic seizure. In the second group, we observed a different response to the stimuli: after the first episode of wild running, the rats had a short pause (7 ± 2 sec) followed by a second episode of wild running (15 ± 3 sec) and tonic-clonic seizure for 21 ± 2 sec. Exposition of EMF we performed in both group of GEPRs.

A low frequency EMF exposure (10000-15000 Hz, 1-1.5 m/Tesla) resulted in full or partial depression of general behavior in both groups of GEPRs. The latency of first wild run significantly increased ($p \leq 0.05$) from 20 ± 7 sec (in control group) to 35 ± 5 sec (in GEPRs, group I) and from 21 ± 4 to 50 ± 2 sec (in GEPRs, group II). The duration of wild run significantly decreased ($p \leq 0.05$) from 14 ± 3 sec (in control group) to 9 ± 3 sec (in GEPRs, group I) and 8 ± 2 to 4 ± 1 sec (in GEPRs, group II) (Figure 3 and 4).

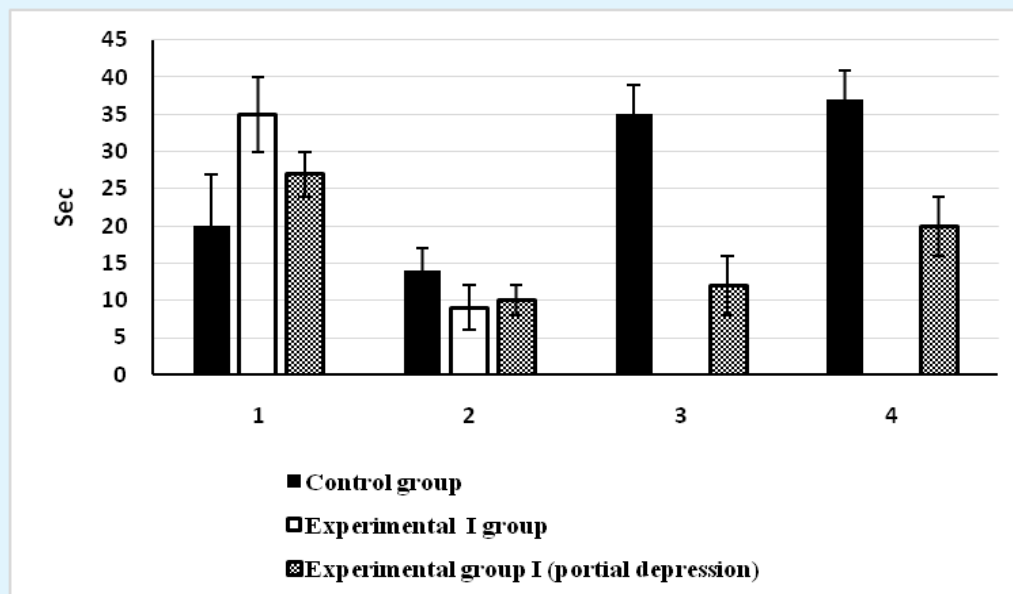


Figure 3: The effect of acoustic range EMF on behavior manifestation of seizure activity in I group of GEPRs.

Black columns – GEPRs (control group). White and Patterned columns –GEPRs with EMF exposure (experimental groups). 1. Latency period for the wild run; 2. Duration of the wild run; 3. Duration of tonic-clonic seizures; 4. Duration of post-ictal activity; 5. Duration of tonic-clonic seizure (partial depression); 6. Duration of post-ictal activity (partial depression).

Group II of GEPRs demonstrated significant increases in the pause between the first and second wild run episodes from 7 ± 2 to 25 ± 11 sec and decreases in the duration of second wild run from 15 ± 3 to 5 ± 2 sec

($p \leq 0.05$). It is noteworthy that EMF exposure resulted in significant prolongation of the wild run pause. This result suggests that EMF exposure causes a reduction of excitability in neuronal circuitry of brain structures involved in audiogenically-induced seizures. Moreover, in experimental II group of rats, the duration of the pause between the first and the second wild run episodes increased significantly. These findings suggest that the pause between wild runs is a manifestation of re-organization of the endogenous mechanisms that are involved in the suppression of seizure development (Figure 4).

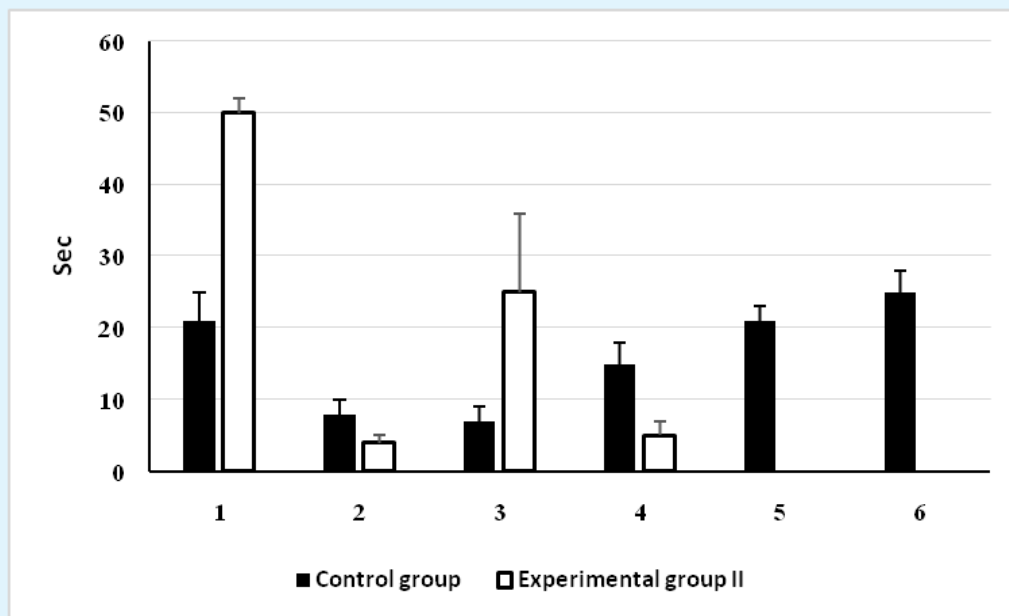


Figure 4: The effect of acoustic range EMF on behavior manifestation of seizure activity in II group of GEPRs.

Black columns – GEPRs (control group). White and Patterned columns –GEPRs with EMF exposure (experimental groups). 1. latency period for the wild run; 2, duration of the wild run; 3. duration of tonic-clonic seizures; 4. duration of post-ictal activity; 5. duration of tonic-clonic seizure (partial depression); 6. duration of post-ictal activity (partial depression).

On the background of EMF exposure Group II of GEPRs did not manifest tonic-clonic seizures. In contrast, some animals of GEPRs Group I (n=2) manifested tonic-clonic seizure activity. In these animals the durations of tonic-clonic seizures and post ictal period of depression decreased from 35 ± 4 to 12 ± 4 sec, and from 37 ± 4 to 20 ± 4 sec, respectively (Figure 3). Our results suggest that I group of GEPRs, the rats that developed only one wild run, have stronger audiogenic seizure activity, compared to Group II of GEPRs. Consequently, EMF fully suppresses seizure activity in Group II of animals. However, a suppression of seizure activity was also been observed in some animals of Group I.

EMF Exposure and ECoG Activity of Sensomotoral Cortex

In Group II of GEPRs, we recorded ECoG activity of sensomotoral cortex with or without EMF exposure. In response to a strong sound (single audiogenic stimuli), we did not see significant changes in ECoG activity of sensomotoral cortex, but we observed clear behavioral seizure activity. Changes in the ECoG activity were

observed following repeated audiogenic stimuli. Right after presenting last sound in GEPRs, we observed ECoG desynchronization. ECoG of sensomotoral cortex was predominately presented by low frequency activity (0-0.5Hz) intermixed with delta (0.5-4 Hz) and theta (4-9 Hz) waves. During pause, the activity was changing back to the background pattern.

On the background of repeated EMF exposure (10000-15000 Hz, 1-1,5 m/Tesla) a repeated audiogenic stimuli did not result in the development of ECoG activity of sensomotoral cortex observed in audiogenically kindling GEPRs and the rats did not manifest seizure activity.

Experimental evidence indicates that inferior colliculus plays a significant role in the development of audiogenic seizure activity. Discharge rate of inferior colliculus neurons, located in the deep part of the structure, increases right before the onset of generalized seizures. The activity of neurons located in the anterior part of the inferior colliculus increases during wild run. It appears that reticular nucleus of the brainstem is involved in the development of clonic-tonic phase of seizure; discharge rate of these neurons significantly increase right before the onset of clonic-tonic phase of seizure. During post-ictal depression, activity of the inferior colliculus is decreased, but the activity of brainstem reticular nucleus maintains on a high level [11-14]. These findings suggest that inferior colliculus and reticular nucleus of the brainstem play different role in the development of seizure activity.

Our results indicate that a single sound presentation does not change ECoG activity of sensorimotor cortex suggesting that sensorimotor cortex is not involved in the development of audiogenic seizures. In contrast, brainstem structures play a significant role in the development of audiogenic seizures. But, the initiation of seizures requires a repeated stimulation of brainstem reticular formation. Besides, rostral part of cortex has significant role in manifestation of seizure activity in audiogenically kindling GEPRs.

Summary and Conclusion

Finding of the present study suggests that low frequency acoustic range EMF exposure is a noninvasive procedure which allows to depress (fully or partially) the seizure activity developed in response to audiogenic stimuli in Krushinsky-Molodkina strain GEPRs. We tried to understand the possible mechanisms by which EMF exposure, with a mentioned field parameters, is capable of having a positive effect on the GEPRs.

In our experiments, brain structures are subjected not only to direct transcranial stimulation, but they also receive afferent signals from the whole body. We suggest that the artificially created EMF may change the tonic activity of brain cortex. The EMF can modulate Ponto-geniculate-occipital (PGO) waves. On the other hand, PGO waves have a possible inhibitory influence on EEG seizure activity [15]. Increased number of PGO spikes in animals exposed to auditory stimulation is attributed to the anatomical proximity of the structures involved in acoustic signal processing. Besides, acoustic stimulation could promote the release of acetylcholine in the brainstem structures involved in initiation of PGO waves. Perhaps, these influences are mediated by changes in membrane ion-channel permeability, which occur under the influence of low frequency EMF [8,6,16]. In addition, we suggest that EMF exposure on brain results in changes in electric and current density fields, accompanied by modification of synaptic activity, modes of synchronous bursts of neuronal populations, ion dynamics and other phenomena. Finally, it will manifest on behavioral and cognitive level.

Thus, proposed biological mechanisms of antiseizure action of EMF exposure in GEPRs might include normalization of neuroendocrine, neurotransmitter, and/or neurotrophic factors.

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