Therapeutic Efficacy of Repetitive Transcranial Magnetic-Electrical Stimulation in Kainic Acid-Induced Epileptic Rats

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Abstract

Objective To investigate the therapeutic efficacy of transcranial magnetic electrical stimulation (TMES) on kainic acid (KA)-induced temporal lobe epilepsy rats. Methods Sixty-two rats were divided into a pretreatment group (total 32 rats) and a treatment group (total 30 rats) using the random number table method. The pretreatment group was further divided into 4 subgroups, which received current stimulation at 0%, 25%, 50%, and 75% of the therapeutic instrument' s maximum current intensity (MCI), respectively, to determine the optimal stimulation parameters under our experimental conditions. The treatment group was further divided into 3 subgroups with 10 rats each. Two groups (epilepsy stimulation group and epilepsy non-stimulation group) were epilepsy model rats that met the inclusion criteria. The stimulation parameters for the stimulation group were the optimal parameters determined by the pretreatment group. Rats in the non-stimulation group received the same pre- and post-stimulation handling as the stimulation group, but the therapeutic instrument had no effective energy output. The third group was a control group of non-modeled control rats. All three groups received stimulation once daily, 40 min/session, for 14 days. Behavioral, electrophysiological, and histological changes were recorded and compared among the three groups to evaluate the therapeutic efficacy of TMES on epilepsy rats. Results 50% MCI was determined as the optimal stimulation intensity. The frequency of epileptic wave occurrence in the epilepsy stimulation group was significantly lower than that in the epilepsy non-stimulation group [(30.210 ± 4.580) times/min vs. (31.380 ± 4.247) times/min], with a statistically significant difference (t=3.235, P=0.001). Timm staining results showed that the difference in staining scores among the three groups was statistically significant (F=17.429, P=0.000). The Timm staining score in the inner molecular layer of the hippocampal dentate gyrus in the epilepsy stimulation group was significantly reduced compared with the epilepsy

non-stimulation group, with a statistically significant difference (P<0.05). Conclusion TMES therapy can influence the formation of dentate gyrus neuronal circuits by ameliorating the degree of histological changes in the inner molecular layer of the hippocampal dentate gyrus in epilepsy rats, thereby reducing the frequency of epileptic brain wave seizures.

Full Text

Therapeutic Effect of Repetitive Transcranial Magnetoelectric Stimulation on Kainic Acid-Induced Epileptic Rats

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Abstract

[**Objective**] To investigate the therapeutic effects of transcranial magnetoelectric stimulation (TMES) on temporal lobe epilepsy rats induced by kainic acid (KA). [**Methods**] Sixty-two rats were divided into pretreatment (n=32) and treatment (n=30) groups using a random number table method. The pretreatment group was further divided into four subgroups, each receiving stimulation at 0%, 25%, 50%, or 75% of the therapeutic device' s maximum current intensity (MCI) to determine optimal stimulation parameters under our experimental conditions. The treatment group was subdivided into three groups of 10 rats each: two groups comprised epilepsy model rats that met inclusion criteria (epilepsy-stimulated group and epilepsy-non-stimulated group), and the third group served as unmodeled controls. The stimulated group received parameters identified as optimal from the pretreatment group, while the non-stimulated group underwent identical procedures but without effective energy output from the device. All three groups received stimulation once daily for 40 minutes over 14 days. Behavioral, electrophysiological, and histological changes were recorded and compared to evaluate TMES efficacy in epileptic rats. [**Results**] Fifty percent MCI was identified as the optimal stimulation intensity. The frequency of epileptic waves in the epilepsy-stimulated group was significantly lower than in the epilepsy-non-stimulated group [(30.210 ± 4.580) beats/min vs. (31.380 ± 4.247) beats/min], with statistically significant difference ($t = 3.235$, $P = 0.001$). Timm staining results revealed significant differences among the three groups ($F = 17.429$, $P = 0.000$), with the epilepsy-stimulated group showing significantly reduced Timm staining scores in the inner molecular layer of the hippocampal dentate gyrus compared to the non-stimulated group ($P < 0.05$). [**Conclusions**] TMES therapy can influence dentate gyrus neuronal circuit for-

mation by ameliorating histological changes in the inner molecular layer of the dentate gyrus in epileptic rats, thereby reducing the frequency of epileptic brain wave discharges.

Keywords: Transcranial magnetoelectric stimulation; Temporal lobe epilepsy; Kainic acid
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For patients with refractory epilepsy (RE) who have clear surgical indications, surgical treatment represents an important therapeutic option, yet 20–30% of patients still experience postoperative recurrence. Additionally, a subset of epilepsy patients lacks clear surgical indications and shows poor response to pharmacological treatment. Consequently, there is an urgent need to explore safe, effective, and non-invasive therapeutic approaches. Transcranial magnetic and electrical stimulation, characterized by non-invasiveness, painless application, simple operation, and relative safety, has been widely applied in research on central and peripheral nervous system disorders, including mood disorders, Parkinson' s disease, Alzheimer' s disease, chronic pain, epilepsy, and neurological rehabilitation. Research in the epilepsy field has garnered increasing attention. This study established a kainic acid (KA) temporal lobe epilepsy model and conducted animal experiments with continuous transcranial magnetoelectric combined stimulation (TMES) during the latent period, employing histological and behavioral experiments to investigate the therapeutic efficacy of TMES in epileptic rats.

1.1 Experimental Animals, Reagents, and Equipment

(1) Experimental Animals: Sixty-two male Wistar rats weighing 220–260 g and aged 6–8 weeks were provided by the Animal Center of Harbin Medical University. All rats were housed under identical lighting and temperature conditions with free access to food and water. Experimental animal use and protection principles were followed throughout the study, with all procedures designed to avoid or minimize animal discomfort. **(2) Major Reagents and Equipment:** Kainic acid (Enzo Life Sciences, USA), gum arabic (Sigma, USA), silver nitrate, sucrose, hydroquinone, citric acid (Xilong Chemical, China), sodium citrate (Sinopharm Chemical Reagent, China), transcranial magnetoelectric therapeutic apparatus (TME-01, constant magnetic field 282 mT, square wave current, Harbin Aobo Medical Apparatus Co., Ltd., China), animal stereotaxic apparatus (Shanghai Yuyan Scientific Instruments, China), optical microscope (Olympus, Japan), and cryostat (Leica, Germany).

The 62 rats were divided into pretreatment (n=32) and treatment (n=30) groups using a random number table method. Rats in the pretreatment group received stimulation at different current intensities before undergoing stereotactic right hippocampal KA injection to induce epilepsy. Optimal stimulation parameters for our experimental conditions were determined through analysis of behavioral observations. Treatment group epileptic rats then received TMES intervention using these parameters, and therapeutic effects were evaluated.

During TMES administration, a multi-turn, multi-point E-shaped coil was positioned with its center aligned to the sagittal suture midpoint, parallel to the parietal bone, ensuring the coil surface remained in close contact with the rat' s scalp. Hair on the affected side temple area was shaved, and TME-01 therapeutic apparatus output electrodes were applied—one on the affected temple and the other on the tip of the nose. Transcranial magnetoelectric stimulation was delivered according to predetermined parameters.

1.3 Pretreatment Group Interventions

The 32 pretreatment rats were further divided into four subgroups (A1, A2, A3, A4) of eight rats each using a random number table method. Each rat received stimulation once daily for 40 minutes over 14 days. All subgroups received magnetic field intensity of 282 mT and stimulation frequency of 10 Hz, with current intensities set at 0%, 25%, 50%, and 75% of maximum current intensity (MCI), respectively. The A1 group (0% MCI) served as the sham stimulation group, receiving "sham" magnetoelectric intervention without energy output from the device.

1.4 Treatment Group Interventions

The treatment group was divided into three subgroups of 10 rats each using a random number table method. Two groups (epilepsy-stimulated group and epilepsy-non-stimulated group) comprised epilepsy model rats meeting inclusion criteria; the stimulated group received optimal parameters identified in the pretreatment group, while the non-stimulated group underwent identical procedures but without effective energy output. The third group served as unmodeled controls. All three groups received stimulation once daily for 40 minutes over 14 days.

1.5 Epilepsy Model Establishment and Behavioral Scoring

Rats in the pretreatment group (A1–A4) and the two treatment groups underwent stereotactic surgery after completing 14 days of pretreatment stimulation or before commencing 14 days of therapeutic stimulation, respectively. A burr hole was drilled at 5.6 mm posterior to the bregma and 4.5 mm lateral to the right of the sagittal suture. A microinjector needle was advanced slowly to a depth of approximately 5.5 mm, and KA/saline solution was injected at 0.2 l/min. The needle remained in place for 5 minutes before slow withdrawal to

establish a right intrahippocampal KA-induced temporal lobe epilepsy model. Control rats received equivalent volumes of saline.

Post-injection behavior was closely monitored, with seizure severity assessed according to Racine' s seizure classification scale (scored 0–5 corresponding to stages 0–V). Rats exhibiting frequent or sustained limb convulsions for over 30 minutes were recorded as status epilepticus. When status epilepticus exceeded 60 minutes, 10% chloral hydrate (350 mg/kg) was administered intraperitoneally to terminate seizures. Rats that died during seizure activity within 60 minutes, or that died despite rescue intervention, were scored as 5.

1.6 EEG Monitoring in Treatment Groups

After completing 14 days of TMES intervention, rats in the epilepsy-stimulated and epilepsy-non-stimulated groups underwent EEG monitoring. Electrode placement was determined stereotactically: the bregma was marked, and a burr hole was drilled 3.8 mm posterior to the bregma and 2.7 mm lateral to the right of the sagittal suture. Deep recording electrodes were slowly inserted to a depth of approximately 3.8 mm. Stainless steel screws were symmetrically fixed to the skull as reference and ground electrodes.

1.7 Brain Tissue Perfusion and Staining

Following deep anesthesia, the chest cavity was opened to expose the heart. A cannula was inserted into the left ventricle, the right auricle was incised, and perfusion was performed sequentially with 200 mL of 0.9% NaCl solution, 200 mL of 0.37% Na S solution, and 200 mL of 4% paraformaldehyde solution. After decapitation, brains were post-fixed in 4% paraformaldehyde at 4°C for 24 hours, then placed in gradient sucrose solution at 4°C until sinking. Before sectioning, brain tissue was mounted on a specimen holder and processed routinely for frozen sectioning at 50 m thickness, which was reduced to 10 m when hippocampal structures appeared. Sections were mounted on polylysine-coated slides and subjected to Timm staining. Staining results were evaluated using Cavazos' criteria to score mossy fiber sprouting (MFS) in the inner molecular layer of the hippocampal dentate gyrus.

1.8 Statistical Methods

SPSS 19.0 was used for statistical analysis. Data are expressed as mean ± standard error. Comparisons between two groups were performed using two-sample t-tests, while multi-group comparisons used one-way ANOVA with LSD-t tests for post-hoc pairwise comparisons. Ranked data were compared using Kruskal-Wallis H tests. $P < 0.05$ was considered statistically significant.

2.1 Comparison of Seizure Severity in Pretreatment Groups

During the observation period following KA injection, pretreatment subgroup rats were scored according to Racine' s seizure classification. Statistical analysis revealed significant differences among the four groups (H = 19.992, P = 0.000). Based on mean rank values, 50% MCI was determined as the optimal stimulation intensity and was used for all subsequent experiments. Details are presented in .

TABLE:1 Seizure severity scores in rats after pretreatment with different current intensities

Group	Current Intensity	Seizure Score
A1	0% MCI	
A2	25% MCI	
A3	50% MCI	
A4	75% MCI	

H = 19.992, P = 0.000; MCI: maximum current intensity.

2.2 EEG Monitoring Results in Treatment Groups

EEG monitoring revealed epileptic waves in both epilepsy-non-stimulated and epilepsy-stimulated groups, as shown in [Figure 1: see original paper]. Quantitative analysis demonstrated that epileptic wave frequency was significantly lower in the epilepsy-stimulated group compared to the non-stimulated group [(30.210 ± 4.580) beats/min vs. (31.380 ± 4.247) beats/min], with statistically significant difference (t = 3.235, P = 0.001).

FIGURE:1 EEG manifestations in Wistar rats after transcranial magnetoelectric therapy. A: Control group; B: Epilepsy-non-stimulated group; C: Epilepsy-stimulated group; * indicates epileptic waves.

2.3 Timm Staining Results

Timm staining reveals mossy fiber sprouting (MFS) in the inner molecular layer of the hippocampal dentate gyrus. After 14 days of TMES treatment, Timm scores were used to evaluate TMES effects on MFS. Control rats showed no Timm staining bands in the dentate gyrus, while epilepsy-non-stimulated rats exhibited prominent black Timm staining bands in the inner molecular layer. In contrast, epilepsy-stimulated rats showed significantly reduced Timm staining intensity. Statistical analysis revealed significant differences among the three groups (F = 17.429, P = 0.000). Details are shown in [Figure 2: see original paper] and [Figure 3: see original paper].

FIGURE:2 Timm staining results in hippocampal dentate gyrus after 14 days of transcranial magnetoelectric stimulation in three groups of rats (×100). A:

Control group; B: Epilepsy-non-stimulated group; C: Epilepsy-stimulated group; black arrows indicate staining bands.

FIGURE:3 Comparison of Timm staining scores in hippocampal dentate gyrus among three groups of rats.

3 Discussion

Epilepsy comprises a group of neurological disorders characterized by highly synchronized, self-limiting abnormal discharges of brain neurons. Approximately 50 million people worldwide suffer from epilepsy, with nearly 80% residing in developing countries. In China, the epilepsy incidence rate is 7‰, and about 30% of patients do not achieve effective control with current antiepileptic drugs —a condition termed refractory epilepsy. Temporal lobe epilepsy represents the most common form of refractory epilepsy, and its treatment remains a major research focus and challenge. The hippocampus plays a central role in its pathogenesis, and pathological changes in temporal lobe epilepsy are closely associated with organic brain injury, leading to morphological alterations in neural tissue. Under normal relaxed conditions, EEG monitors waves at 8–13 Hz. Based on electrophysiological and histological foundations of epilepsy, we hypothesized that weak magnetic microcurrent stimulation at 10 Hz could induce and increase rhythm activity. Using the TME-01 transcranial magnetoelectric therapeutic apparatus, this study applied combined transcranial magnetic and electrical stimulation to epileptic rats and found that appropriate stimulation parameters could improve seizure severity, reduce epileptic brain wave frequency, and influence histomorphological changes in epileptic rat brains.

3.1 TMES Reduces Abnormal EEG and Seizure Frequency

Our findings demonstrate that epileptic rats have an optimal stimulation current for TMES therapy. During the effective treatment period, TMES significantly reduced epileptic wave frequency compared to controls. Previous studies have shown that pretreating epileptic rats with different magnetic-electric output frequencies and intensities can interfere with seizure thresholds, delay seizure onset, and reduce seizure severity. In 2013, Liu et al. reported successful treatment of two patients with focal refractory status epilepticus using transcranial magnetic stimulation, with markedly reduced seizure frequency and decreased spike wave counts on EEG analysis, even after discontinuing pentobarbital and reducing phenobarbital dosage. Wei et al. demonstrated that navigated transcranial magnetic stimulation provides reliable evidence for functional zone mapping in epilepsy surgery. Thus, transcranial magnetic stimulation not only reduces abnormal epileptic EEG activity and clinical seizure frequency but also can be combined with other techniques for preoperative epilepsy evaluation. Additionally, Liu et al. achieved promising results using transcranial electrical stimulation in temporal lobe epilepsy treatment.

Unlike high-voltage, low-frequency pulsed magnetic field stimulation used in

previous studies, our experiment employed a weak magnetic microcurrent stimulation mode to explore TMES effects on epileptic rats. Results indicate that optimal stimulation current can reduce abnormal discharges in epileptic foci and decrease seizure frequency. Furthermore, high-frequency microcurrent combined with weak magnetic stimulation did not produce "electrical kindling" effects that could induce or aggravate epilepsy, further supporting the potential value of TMES in epilepsy treatment and establishing a foundation for neuromodulation therapy using weak magnetic microcurrent stimulation.

3.2 TMES Improves Histological Changes in Epileptic Rat Brains

Hippocampal mossy fibers are axons of dentate gyrus granule cells that normally form synaptic connections with CA3 pyramidal cells. Under physiological conditions, very few mossy fibers project recurrent axonal branches into the inner molecular layer. However, in hippocampal sclerosis, extensive mossy fiber collaterals project to the dentate gyrus inner molecular layer, establishing excitatory synaptic connections with granule cell dendrites and spines. In epileptic hippocampi, mossy fibers lose their normal target connections and aberrantly sprout into the dentate gyrus inner molecular layer, creating recurrent excitatory circuits. Electron microscopy reveals that MFS forms asymmetric excitatory connections with granule cell dendritic spines in temporal lobe epilepsy models. Studies have shown that MFS correlates highly with spontaneous seizure frequency and represents an important feature of epileptogenesis, with sparse MFS detectable in the dentate gyrus 4 days after status epilepticus induction, reaching stable levels by approximately 100 days. Timm staining can detect sparse MFS 7 days after status epilepticus. Based on this theoretical foundation, we detected moderate MFS in eligible epileptic rats on day 14. Using specific Timm histochemical staining, we observed mossy fiber sprouting in the hippocampal formation and dentate gyrus inner molecular layer of temporal lobe epilepsy rats. TMES treatment significantly improved MFS severity in epileptic rat hippocampi and dentate gyrus, with statistically significant differences.

3.3 Possible Mechanisms of TMES in Epilepsy Treatment

The mechanisms underlying TMES therapy for epilepsy remain inconclusive but may involve regulation of endogenous neurotransmitters, changes in brain tissue metabolic rate, and alterations in ion channel structure and function. Our study confirmed that continuous TMES treatment with appropriate parameters, while not completely preventing spontaneous seizures, effectively reduced aberrant mossy fiber sprouting in the hippocampal CA3 region and decreased epileptic brain wave frequency. Based on the relationship between epileptogenesis and MFS, we hypothesize that TMES reduces epileptic discharge frequency and prevents seizure occurrence by improving MFS severity in the dentate gyrus inner molecular layer during epileptogenesis, thereby influencing dentate gyrus neuronal circuit formation. This animal study preliminarily explored the potential value of weak magnetic microcurrent TMES for epilepsy treatment and

provided new insights and possibilities for clinical application. However, the specific mode of neuronal circuit regulation requires further investigation. Additionally, issues such as minimizing external electromagnetic interference during treatment, improving clinical safety, determining interactions between magnetic and electrical components during therapy, identifying dominant factors, and elucidating underlying mechanisms require strengthened multidisciplinary collaboration, multicenter clinical studies, and further animal experiments.

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Author Contributions:

Zhang Wang, Wang Xiaoyi, Guo Hongqu, and Song Yuanyuan: Conducted experiments and analyzed data.

Shen Hong: Conceived the study, designed the research protocol, drafted and revised the manuscript.

Wang Aili: Developer of the transcranial magnetoelectric therapeutic apparatus, participated in manuscript drafting.

Sun Zuodong: Conceived the study, designed the research protocol, inventor

of the transcranial magnetoelectric therapeutic apparatus, revised the final manuscript.

Note: Figure translations are in progress. See original paper for figures.