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FULL-LENGTH ORIGINAL RESEARCH

Effects of Noninvasive Transcutaneous Electrical Stimulation via Concentric Ring Electrodes on Pilocarpine-induced Status Epilepticus in Rats

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SUMMARY

Purpose: **The aim of this pilot study was to investigate the antiepileptic effects of a novel noninvasive stimulation technique, transcutaneous electrical stimulation (TcES) via scalp concentric ring electrodes, on pilocarpine-induced status epilepticus (SE) in rats.**

Methods: **Five minutes after the onset of SE, TcES was administered to the experimental rat via bipolar concentric ring electrode at the CZ location. Symmetrical, biphasic, charge-balanced, constant current, isolated pulses were applied via a custom-made stimulator. TcES parameters ranged from 200–750 Hz, 200 or 300 μs pulse duration, and 50 or 60 mA, applied for 1 min, started with the least intense parameter set and progressively increased.**

Results: **TcES attenuated electrographic seizure activity and halted the progression of behavioral seizures. Interruption of seizure activity outlasted the period of stimulation and appeared to be long-lasting. TcES treatment significantly extended the life and enhanced the survival of rats after SE.**

Conclusions: **Noninvasive TcES, applied 5 min after SE onset via novel concentric ring electrodes on the scalp, reduced, or abolished electrographic and behavioral seizure activity in pilocarpine-induced SE in rats. These findings suggest that TcES may have a role in the treatment of SE.**

KEY WORDS: **Status epilepticus—Transcutaneous electrical stimulation—Concentric ring electrodes—Pilocarpine-induced seizures.**

Approximately 25% of epilepsy patients suffer from intractable seizures despite medical treatment (Epilepsy Foundation). One important consequence of medically intractable epilepsy is an increased incidence of status epilepticus (SE) (Sillanpaa and Shinnar, 2002). Uncontrolled seizures, over time, are associated with cognitive and progressive behavioral disturbance, increased morbidity and mortality, and sudden accidental deaths.

We conducted a preliminary investigation on the antiepileptic effects of a novel noninvasive stimulation technique, transcutaneous electrical stimulation (TcES) via bipolar concentric ring electrodes, using the pilocarpine-induced SE model in rats. Concentric ring electrodes have unique capabilities (Besio et al., 2006a, 2006b) in the recording mode as they yield the second spatial derivative, i.e., the Laplacian, of the surface potentials. When used to stimulate, concentric ring electrodes allow the electric field to be more focused into the tissue than conventional disc electrodes (Van Oosterom and Strackee, 1983). Unlike transcranial electrical stimulation (TES), in which stimulation is applied across the head, TcES via concentric ring electrodes stimulates directly below a particular electrode. We applied TcES to the scalp and tested its effects on behavioral and electrographic activity due to pilocarpine-induced SE.

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METHODS

Experiments were conducted in accordance with an animal protocol approved by Louisiana Tech University IACUC. Male Sprague-Dawley rats (280–330 g) were

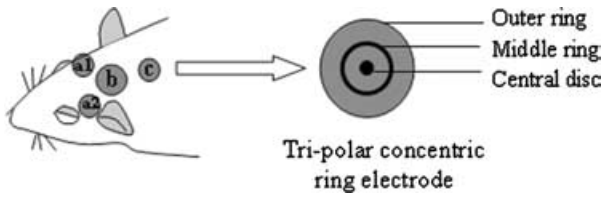

Figure 1.
Three tripolar concentric ring electrodes placed on the rat scalp at locations (a1) and (a2), diameter = 0.6 cm, location (b), diameter = 1.0 cm and a reference electrode at location (c), diameter = 0.6 cm.

housed in a temperature-controlled environment with a 12 h light/dark cycle and given food and water ad libitum.

Animal preparation

Rats were anesthetized with ketamine (120 mg/kg, i.p.). The scalp was shaved and prepared with NuPrep abrasive gel (D. O. Weaver & Co., Aurora, CO, U.S.A.). Three custom-designed tripolar concentric ring electrodes (Besio et al., 2006a) were applied to the scalp using conductive paste (0.5 mm Ten20, Grass Telefactor, RI, U.S.A.) and adhered with Teets dental acrylic (Pearson Lab Supply, Sylmar, CA, U.S.A.). As shown in Fig. 1 location (b), one tripolar concentric ring electrode (diameter = 1.0 cm) was placed at the center of the head corresponding to CZ of the 10/20 international electrode placement system; the other 2 tripolar concentric ring electrodes [locations (a1) and (a2), diameter = 0.6 cm] were placed on both sides that would correspond to C3 and C4 of the 10/20 international electrode placement system. A reference electrode [location (c), diameter = 0.6 cm] was attached on the top of the neck behind the ears. The electrodes were made of gold-plated copper and each ring was 0.9 mm wide. Rats were returned to their cages and allowed food and water ad libitum for approximately 24 h until the experimental procedure began.

Experimental procedure

Scopolamine methylnitrate (2 mg/kg, i.p., Sigma, St. Louis, MO, U.S.A.) was administered to prevent peripheral cholinergic effects such as respiratory distress and dehydration. A flexible shielded cable was connected to the electrodes and the skin-to-electrode impedance was measured and kept less than 10 kOhm. Twenty minutes after the administration of scopolamine methylnitrate, electroencephalogram (EEG) recording was started, using 2 bipolar channels for each concentric ring electrode, one for the outer ring and disc difference and the other for the middle ring and disc difference. This is in fact Laplacian EEG although we will continue to refer to it as EEG throughout this article. The EEG signals were preamplified (gain 100 and 0.3 Hz high pass filter) with a custom built preamplifier and then amplified using a Grass Model 15 LT Bipolar Portable Physiodata Amplifier System (Grass Telefactor) with a gain of 1,000 and band pass of 1–30 Hz with the 60 Hz notch filter active and digitized (16 bits, 250 s/s). Thirty minutes after the administration of scopolamine methylnitrate, pilocarpine HCl (310 mg/kg, i.p., Sigma) was injected. Behavior was documented with continuous video monitoring.

Administration of TcES

Following the report by Goodkin et al. (2003), the seizure activity was considered to have reached SE when there was continuous electrographic activity for at least 30 s during the waxing and waning stage. Rats were randomly assigned to one of 2 groups: control (n = 8) and experimental (n = 8). Symmetrical, biphasic, charge-balanced, constant current TcES pulses were applied to experimental rats via a custom-made stimulator. Control rats did not receive TcES.

Five minutes after the onset of SE, TcES was delivered via the outer ring and disc (with the middle ring floating) of the electrode at location (b) shown in Fig. 1. The range of TcES parameters used was 200, 300, 500, or 750 Hz, 200 or 300 μs pulse duration, and 50 or 60 mA intensity, applied for 1 min. This range of parameters was selected based on previous reports on intracranial electrical stimulation for epilepsy (Gilman et al., 1975; Velasco et al., 1996; Kerrigan et al., 2004; Kossoff et al., 2004; Theodore and Fisher, 2004). TcES was started with the least intense parameter set (200 Hz, 200 μs pulse width, 50 mA) and progressively increased. If no change was observed in the electrographic or behavioral activity 5 min after the administration of TcES, another pulse train with the next higher frequency was applied, increasing up to 750 Hz. If there was still no evident change in electrographic or behavioral activity (n = 4), the pulse width was increased (300 μs) and then the current (60 mA). A 5-min pause was taken between each TcES administration to evaluate its effects on the electrographic activity and behavioral manifestations. This 5-min pause was adopted from reported protocols for evaluating the antiepileptic effects of intracranial electrical stimulation (Theodore and Fisher, 2004).

Experiments were also conducted to compare the effects of conventional TES and TcES on motor activity in naive rats (n = 3). The same animal preparation procedure described previously was followed to place the electrodes. Stimulation (500 Hz, 200 μs pulse duration, 50 mA) was applied for 1 min. For TES, the stimulation was applied through 2 conventional disc electrodes (diameter = 0.9 cm) placed at locations (a1) and (a2) of Fig. 1. For TcES, 2 methods were tested: (1) stimulation was applied between the outer ring and central disc of a concentric ring electrode (diameter = 1.0 cm) placed at location (b) of Fig. 1; (2) stimulation was applied between the outer ring and central disc of 2 concentric ring electrodes

(diameter = 1.0 cm) placed at locations (a1) and (a2) of Fig. 1. In case (2), the total current for the concentric ring electrodes (100 mA) was twice that of the disc electrodes.

To verify that TcES did not cause respiratory complications, we applied TcES to five naive rats and visually monitored respiration. TcES (500 Hz, 200 μs pulse duration, 50 mA, for 1 min) was applied between the outer ring and central disc of a concentric ring electrode (diameter = 1.0 cm) placed at location (b) of Fig. 1. These stimulation parameters were chosen because they showed preliminary effectiveness in seizure control. The rats were visually monitored intermittently for 48 h.

Assessment of behavioral manifestations

Behavioral manifestations of seizure activity were scored according to a scale adapted from Racine (1972): R = 0, no motor seizure activity; R = 1, eye closure and masticatory movements; R = 2, head nodding; R = 3, mild forelimb clonus; R = 4, clonus with rearing; and R = 5, clonus with rearing and falling. In addition, we included a sixth stage: R = 6, wild running fit since it occurred frequently before the expiration of rats in our experiments. A researcher not involved with the experiments reviewed the videotapes to determine the Racine behavioral stages and the times that they occurred.

Data analysis

The effects of TcES were assessed on 4 measures, electrographic activity, behavioral manifestations, mortality (how long the rats lived after the administration of pilocarpine), and survival status (the life/death status of the rats 24 h after the administration of pilocarpine). To assess electrographic changes, the control group was compared to the experimental group; within the experimental group, comparison was made before and after the administration of TcES. The results are reported as mean ± standard deviation unless otherwise stated.

The nonparametric Mann-Whitney *U* test was used to statistically compare behavioral manifestations between the control group and the experimental group. Two-Sample *t*-tests were used to compare mortality (one-tail) and SE onset time (two-tail) between the control group and the experimental group, respectively. The SAS Proc LIFETEST was used to calculate Kaplan–Meier survival and estimate the distribution of survival time. The SAS Proc PHREG was used to model time to event data via Cox regression and obtain the hazard ratio. Survival plots of the data showed that the proportional hazard assumption was adequate.

RESULTS

Electrographic activity

Control group

The electrographic activity recorded from the scalp surface of the control rats (n = 8) progressed through the classical seizure stages of pilocarpine-induced SE reported by others (Turski et al., 1983; Treiman et al., 1987; Walton and Treiman, 1988). SE onset started 10–29 min (19.5 ± 6) after the administration of pilocarpine. Typically, 10 min after SE onset, continuous spiking activity began and lasted 4–7 h before periodic epileptiform discharges (PEDs) were seen on a relatively flat background. This was true for all except 2 control rats that died before showing PEDs. Fig. 2 shows the EEG recorded from 2 tripolar electrodes during A: baseline, B: 4 m 35 s after SE onset, C: 6 m after SE onset, D: 10 m 35 s after SE onset,

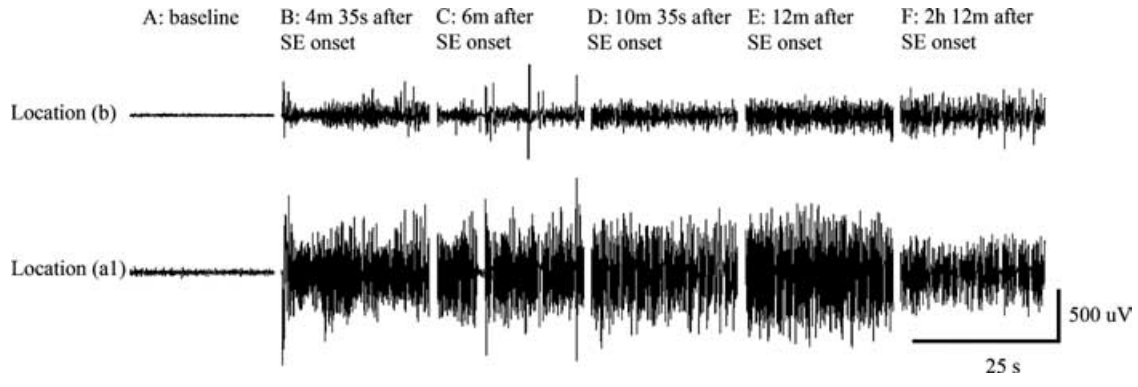

Figure 2.
EEG recorded from 2 tripolar concentric ring electrodes placed at locations (b) and (a1) on the scalp of a control rat. A: baseline, B: 4 m 35 s after SE onset, C: 6 m after SE onset, D: 10 m 35 s after SE onset, E: 12 m after SE onset, and F: 2 h 12 m after SE onset. The times refer to the starting time of each of the 25 s segments shown. For comparison, each of the 25 s segments shows the electrographic activity recorded from a control rat at the same times as from an experimental rat in Fig. 3.

E: 12 m after SE onset, and F: 2 h 12 m after SE onset. The times refer to the starting time of each of the 25 s segments shown. Continuous seizure electrographic activity is observed in B through F.

Experimental group

The baseline electrographic activity of the experimental group (n = 8) was similar to that of the control group. SE onset started 19–40 min (27 ± 8) after the administration of pilocarpine, which was not statistically different from that of the control group (p = 0.198, two-sample *t*-test).

Electrographic activity was attenuated in all 8 experimental rats after 1–3 applications (1.9 ± 0.8) of TcES. In 7 rats, the electrographic activity appeared to have returned to the prepilocarpine baseline after (3.6 ± 1.1) TcES applications. Among them, 2 experienced respiratory problems (probably caused by improper administration of scopolamine methylnitrate) shortly after the injection of pilocarpine and died prematurely (1.0 and 1.25 h after SE onset). However, it appeared that, before expiration, the electrographic activity of these 2 rats was reverting to baseline. One rat presented mostly baseline with some spiking activity for several hours. Attenuation of electrographic activity was consistent from rat to rat, starting with an increase in the interictal period followed by lowered ictal spiking frequency. TcES treated rats never showed PEDs as the control group did. Fig. 3 shows the EEG recorded from 3 tripolar concentric ring electrodes placed on the scalp surface of an experimental rat. Each trace was formed by combing the 2 bipolar signals from each electrode per the method by Besio et al. (Besio et al., 2006a). Fig. 3 shows A: baseline, B: 4 m 35 s after SE onset and before TcES treatment 1 (200 Hz, 200 μs pulse duration, 50 mA for 1 min), C: 6 m after SE onset and immediately after TcES treatment 1, D: 10 m 35 s after SE onset and before TcES treatment 2 (300 Hz, 200 μs pulse duration, 50 mA for 1 min), E: 12 m after SE onset and immediately after TcES treatment 2, and F: 2 h 12 m after SE onset and 2 h after TcES treatment 2. The times refer to the starting time of each of the 25-s segments shown.

The Grass amplifiers used for this research saturate at ±5 V. The maximum signal allowable without clipping with a gain of 100,000 is ±50 μV. The tripolar method by Besio et al. (2006a) multiplies one of the bipolar signals by a factor of 16, giving a range of ±800 μV for the displayed signals. Therefore, the signals shown in Figs. 2 and 3 are approximately 16 times the recorded signals. The signal from the electrode at location (b) has some instances of clipping in Fig. 3 during C and D.

The same rats previously evaluated electrographically were also assessed for behavioral activity. All control rats and experimental rats displayed visually evident behavioral seizure activity 1–5 min after the administration of pilocarpine. The behavioral manifestations all started with R = 1, eye closure and masticatory movements along with R = 2, head nodding.

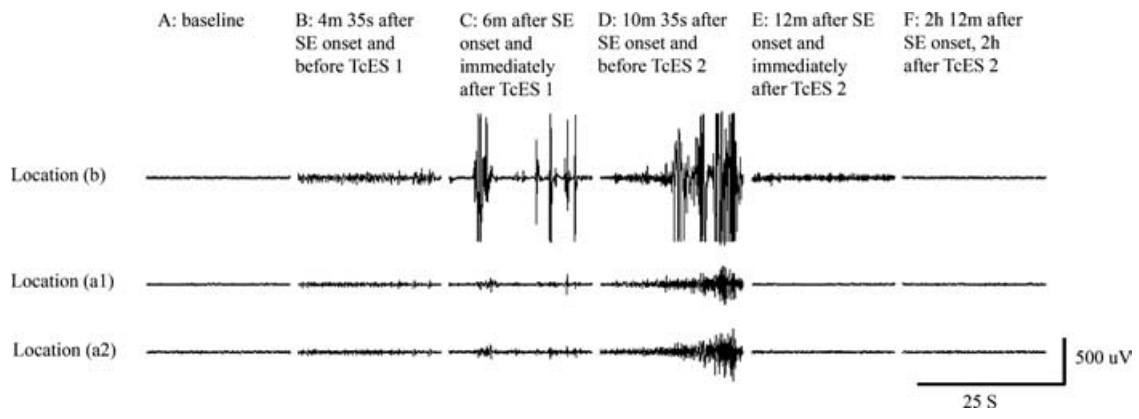

Figure 3.
EEG recorded from 3 tri-polar concentric ring electrodes placed at locations (b), (a1), and (a2) on the scalp of an experimental rat. A: baseline, B: 4 m 35 s after SE onset and before TcES treatment 1 (200 Hz, 200 μs pulse duration, 50 mA for 1 min), C: 6 m after SE onset and immediately after TcES treatment 1, D: 10 m 35 s after SE onset and before TcES treatment 2 (300 Hz, 200 μs pulse duration, 50 mA for 1 min), E: 12 m after SE onset and immediately after TcES treatment 2, and F: 2 h 12 m after SE onset and 2 h after TcES treatment 2. The times refer to the starting time of each of the 25 s segments shown. The seizure electrographic activity is present in B, C, and D. During severe behavioral activity in C and D, the signals from location (b) were clipped. In E, the electrographic activity immediately after TcES treatment 2 resembles the baseline recording. In F, it appears that baseline activity still persists 2 h after TcES treatment 2.

Control group

Five minutes after SE onset, of the 8 control rats, 4 reached R = 4, 2 reached R = 5, and 2 reached R = 6. Seven (87.5%) control rats died shortly after reaching R = 6. The eighth (12.5%) control rat demonstrated continuous behavioral activity but did not reach R = 6 before being killed 43 h after the administration of pilocarpine.

Experimental group

In the experimental group, 5 min after SE onset and immediately before the administration of TcES, 2 rats reached R = 4 and 6 reached R = 5. Shortly after the application of TcES, in 7 of the 8 (87.5%) experimental rats, behavioral activity returned to R = 0, no motor seizure activity. The last (12.5%) experimental rat converted to subtle motor seizure symptoms, R = 2, for several hours before eventually returning to R = 0.

None of the experimental rats ever reached R = 6, whereas 7 of the 8 (87.5%) control rats did, suggesting that TcES halted the progression of the seizures. The difference in seizure behavioral progression between the control and experimental groups was statistically significant (p = 0.0014, Mann-Whitney *U* test).

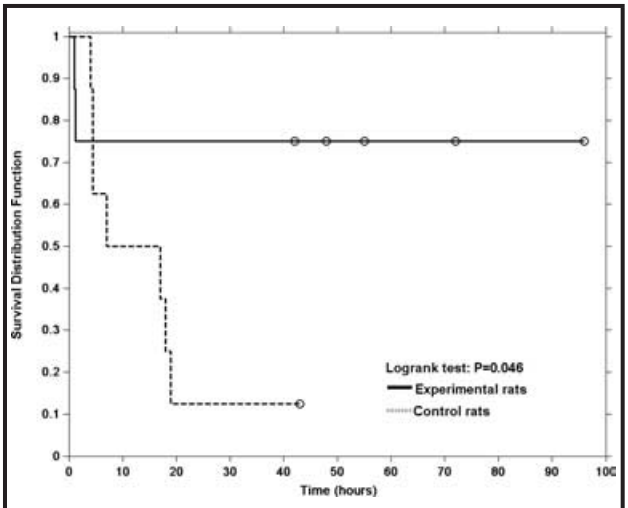

Figure 4.
Kaplan–Meier survival curves for the control rats (dashed) and experimental rats (solid). The circular markers represent censored data.
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Mortality and survival status

Since we do not have facilities for long-term care of the rats, we euthanized them prematurely on average 48 h after the administration of pilocarpine. We calculate the mean time of survival as the time to death or censoring. The mean for the experimental rats is underestimated because of censoring. The control rats expired on average 15 h (14.6 ± 13.2) after the administration of pilocarpine. In contrast, the experimental rats (including the 2 that died prematurely because of respiratory complications) lived on average for 48 h (48.4 ± 33.7), significantly longer than the control rats (p = 0.013, one-sided two-sample t-Test).

Twenty-four hours after the administration of pilocarpine, 6 (75%) of the experimental rats versus one (12.5%) of the control rats were alive. The logrank test for homogeneity indicates a significant difference between the control and experimental rats' survival times (p = 0.046). The Cox proportional hazards ratio of the hazard functions between the 2 groups is 0.22, implying that the hazard function for the experimental rats is smaller than for the control rats. Kaplan–Meier survival curves for the control and experimental rats are shown in Fig. 4.

Other important observations

TcES via concentric ring electrodes, even with twice as much current applied as with TES via conventional disc electrodes, did not cause strong tonic contractions. The rats stimulated via concentric ring electrodes did not elicit aversion responses or escape behavior (e.g., jumping, struggling, vocalizations) as with stimulation from conventional electrodes. Electrographic activity after TcES did not look particularly different from before TcES. TcES-treated rats continued exploring even while the TcES was being applied and resumed eating and drinking after TcES ended. In contrast, TES caused strong tonic contractions as well as rearing and falling and left the rats incapacitated for several minutes. Post-TES electrographic activity showed after-discharges and spiking. No respiratory complications were observed in the rats receiving TcES, whereas those receiving TES appeared to have much lowered respiratory rates, gasping for several minutes after the stimulation. No damage was observed to scalp tissue from either TcES or TES.

Discussion

Effects of TcES on pilocarpine-induced SE

The main finding of our study is that TcES, when applied 5 min after SE onset, stopped or attenuated pilocarpine-induced electrographic and behavioral seizure activity and stopped the seizures from progressing to PEDs. The attenuation appeared to be long-lasting and was associated with resumption of normal feeding and exploratory activity. When comparing the seizure behavioral stages between the control and experimental rats, we observed that the experimental rats never proceeded to R = 6, suggesting that TcES halted the progression of behavioral seizures. This result was especially encouraging, since 6 of the 8 (75%) experimental rats had already reached R = 5 before the administration of TcES.

Administration of TcES

Since this was an exploratory study to test the feasibility of TcES, the stimulation protocol evolved when

improvement was necessary. Our results need to be evaluated in this context. We used a ramp stimulation protocol. If initial TcES parameters did not achieve obvious positive effects in the electrographic or behavioral activity, we proceeded to a more intense parameter set. Since we always started TcES with 200 μs pulse durations, the results with 300 μs pulse duration were confounded. In 2 of the 4 rats that received 300 μs pulse duration, there was further attenuation in the electrographic activity. Increasing the current from 50 to 60 mA had an effect in one of 3 rats. We did not observe complications such as after discharges as a result of TcES administration.

Stimulation via concentric ring electrodes versus via conventional disc electrodes

TcES via concentric ring electrodes did not cause any visible contractions in the rats, whereas TES via conventional disc electrodes caused strong tonic contractions. One possible explanation is that the concentric ring electrode stimulation pattern is much more focused (Van Oosterom and Strackee, 1983), whereas stimulation via disc electrodes broadly activates large volumes of tissue.

Relevance to other brain stimulation techniques

It is not clear why electrical stimulation of the brain has antiepileptic effects. It appears that the stimulus frequency plays a major role in stimulation-induced disinhibition of seizure-gating networks (Lado et al., 2003). High-frequency electrical stimulation may induce a functional lesion-like effect, either imposing a depolarization block or preferentially activating inhibitory neurons (Benazzouz and Hallet, 2000).

The TcES effect on pilocarpine-induced seizures is in line with reports on other techniques of noninvasive and invasive brain stimulation. High-frequency AC fields have suppressed spontaneous epileptiform activity in vitro for up to several minutes after the termination of the stimulation (Bawin et al., 1986b; Bikson et al., 2001; Lian et al., 2003), whereas DC fields suppressed epileptiform activity in vitro only for the duration of the stimulation (Bawin et al., 1986a). By contrast, repetitive transcranial magnetic stimulation (rTMS) increases the time to onset of pentylenetetrazol-induced seizures in rats (Akamatsu et al., 2001). rTMS and preemptive low-frequency AC stimulation applied directly to the amygdala both demonstrated antikindling affects (Anschel et al., 2003; Goodman et al., 2005). In addition, there was evidence that tDCS may have an antiepileptic effect in humans (Fregni et al., 2006).

Interestingly, TcES via concentric ring electrodes showed antiepileptic effects similar to diazepam during the early stages of pilocarpine-induced SE in rats (Goodkin et al., 2003). TcES also appeared to cause long-lasting suppression of seizure activity. It remains unclear whether there is a critical time window for the application of TcES or whether these effects will hold at later stages of SE.

In conclusion, this pilot study showed preliminary evidence that noninvasive TcES via novel concentric ring electrodes, applied 5 min after SE onset, reduced or abolished electrographic and behavioral activities of pilocarpine-induced SE in rats. TcES treatment significantly reduced the mortality of rats after SE. These findings are encouraging and support the need to further investigate the antiepileptic effects of TcES. Further studies will be required to determine what TcES parameters will be consistently effective and safe in attenuating early as well as later stages of SE.

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