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Possible therapeutic effects of transcutaneous electrical stimulation via concentric ring electrodes

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Summary

Even with the latest advancements in antiepileptic drugs (AEDs) there are still many persons whose seizures are not controlled. There are also side effects reported associated with the AEDs. Electrical stimulation of the brain has shown promise toward controlling seizures. However, most brain stimulation techniques involve invasive procedures to implant electrodes and electronic stimulators. There are no conclusive descriptions of where to place the implanted electrodes to control seizures. Noninvasive electrical stimulation does not require the risks of implantation, and the electrodes can be moved easily as needed to determine where they may be the most effective in reducing seizure activity. Herein we review the progress of our group in the development of noninvasive electrical stimulation via concentric ring electrodes to control seizures in rats induced by penicillin G, pilocarpine, and pentylenetetrazole (PTZ).

KEY WORDS: Epilepsy, Penicillin G, Pentylenetetrazole, Pilocarpine, Seizure.

Brain stimulation is a promising new technology for the treatment of medically intractable epilepsy. However, the majority of brain stimulation techniques currently practiced or explored are invasive [for a review on various brain stimulation techniques for epilepsy see (Theodore & Fisher, 2004)]. Electrical stimulation of the brain has a prolonged history. Over the last 30 years, applications have included cerebellar stimulation (Davis, 2000), vagus nerve stimulation (VNS) (George et al., 2000; Patwardhan et al., 2000), which does not directly stimulate the brain, and more recently, deep brain stimulation (DBS), targeting sites such as the subthalamic nucleus (Chabardes et al., 2002), mesial temporal structures (Vonck et al., 2002), and the anterior thalamic nucleus. Other techniques have included trigeminal (DeGiorgio et al., 2003) and glossopharyngeal nerve stimulation (Patwardhan et al., 2002).

Efforts have also been undertaken to interrupt epileptic seizures noninvasively via transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and using electroconvulsive therapy (ECT). TMS applies magnetic fields to the cranium, producing electric fields in the brain. TMS has been studied extensively over the last decade with mixed results for controlling seizures. In a recent study TMS showed effectiveness where the seizure focus could be localized in the neocortex for malformations of cortical development (Fregni et al., 2006a). In a recent pilot study (Fregni et al., 2006b) on patients with malformations of cortical development and refractory epilepsy it has been shown that tDCS decreased epileptic discharges. However, the decrease in seizures due to tDCS was not significant for patients with multiple foci. In ECT, a controlled seizure is induced by applying electrical pulses to the patient's head. A case study reported that ECT acutely controlled seizures in two children (Griesemer et al., 1997).

We have been developing transcutaneous electrical stimulation (TcES) via concentric ring electrodes as an alternative/complementary therapy for seizure control. This innovative noninvasive stimulation technique demonstrated excellent efficacy with both penicillin and pilocarpine (PILO) –induced rat seizure models (Besio et al., 2005, 2007).

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Penicillin

For penicillin G–induced seizures myoclonic jerks began within 1.5 min after the injection of the convulsant, and when the myoclonic jerks reached, on average, 41 per min, monophasic positive pulses, 5–40 mA, at 6–200 Hz for a duration of one minute were applied multiple times. The main result was that the first administration of TcES reduced the myoclonic jerk rate in half. In all instances, after TcES, myoclonic jerks stopped for a few minutes and then returned with a weaker amplitude and a lower frequency. In 13 of the 17 cases, repeated stimulation led to complete cessation of myoclonic jerks. In the control group (n = 8), the myoclonic jerks were continuous with a maximum average rate of 70 per min.

Pilocarpine

For the PILO-induced seizures, 5 min after the onset of SE, TcES was delivered from a tripolar concentric ring electrode centered on the top of the head. Immediately after the application of TcES, attenuation of electrographic seizure activity was evident in all eight treated rats. In some cases, the EEG still resembled the baseline activity, even 2 h after the administration of TcES, whereas the PILO was still active. The behavioral activity of the control group (n = 8) progressed to significantly higher Racine scores than the experimental group (mean R = 5.875 vs. R = 4.75, where R = 6, wild running fit was the maximum possible score). The behavioral manifestations of the treated rats indicate that TcES halted the progression of the seizures. There also was a significant difference between the survival times of the controls and TcES-treated rats. These findings suggest that TcES administered 5 min after SE onset has a significant effect on PILO-induced SE electrographic and behavioral activity, and the effect appears to be long lasting.

Pentylenetetrazole

To evaluate possible therapeutic effects of TcES on seizures induced by pentylenetetrazole (PTZ) in rats, male Sprague-Dawley rats weighing 240–330 g were briefly anesthetized, shaved, and concentric ring electrodes were attached to their scalp 1 day before the experiment. PTZ (45 mg/kg) was given intraperitoneally. Laplacian EEG was recorded from tripolar concentric electrodes on the scalp. TcES (50 mA, 300 Hz, 200 μS for 2 min) was applied directly after the first myoclonic jerk (R = 3). Control rats were prepared and treated the same way, except that no current was passed through the electrodes. Behavior was scored as follows: the stages are: R = 0, no seizure activity; R = 1, oral-facial movements only; R = 2, head nodding; R = 3, myoclonic jerks; R = 4, forelimb clonus; R = 5, rearing (Racine, 1972). The duration of the behavioral signs of seizure activity was measured as time elapsed between the first and last myoclonic jerk. For a within-subjects comparison, the TcES-treated rats were also tested as controls 1–2 days after the TcES treatment.

Table 1. Duration of myoclonic activity

	Duration (min)	
Experiment	Control	TcES
1	31.00	2.00
2	13.00	5.30
3	6.67	2.00
4	10.00	0.68
5	6.50	14.62
6	33.00	19.18
7	9.83	5.37
8	6.65	10.83
9	21.83	6.50
10	46.83	14.50
11	17.13	6.50
12	12.00	0.44
13	20.62	1.75
14	19.83	11.37
15	14.58	NA
16	35.00	NA
17	6.00	NA
18	34.00	NA
19	54.78	NA
20	1.30	NA
21	4.93	NA
Mean	19.14	7.22
SD	12.15	6.03

SD, standard deviation.

In the PTZ control group, the rats exhibited myoclonic jerks (R = 3) with a latency of less than 5 min and then progressed from myoclonic jerks through rearing with forelimb clonus; repeated seizure episodes were observed over a 20-min period. Electrographic signs of seizure activity (short high-frequency bursts in EEG) preceded the behavioral activity and typically continued for over an hour after the behavioral seizure activity had ceased. The duration over which myoclonic jerks occurred (Table 1) was compared between the control group and the TcES-treated group. There was a significant (p = 0.001) reduction in this duration as a result of treatment: TcES treated, 7 min (n = 14) versus controls, 19 min (n = 21). After TcES, no behavioral activity was evident in six treated rats and only a few myoclonic jerks were observed in the remaining treated rats. In most of the treated rats, the electrographic seizure activity was significantly reduced within 1 min after TcES application.

Discussion

TcES applied through the scalp via concentric ring electrodes significantly attenuated seizures induced by

PTZ. The TcES was administered after the first myoclonic jerk (R = 3), which came well after the first signs of electrographic seizure activity. In each of the seizure models we have tested—penicillin, PILO, and PTZ—the TcES was administered after the seizure process had manifested itself by a clear change in behavioral activity (R > 0). In our future studies we will include administering TcES before PTZ administration and also at the first onset of PTZ-induced electrographic seizure activity.

We also found that TcES did not cause motor contractions as is common with electroconvulsive therapy, another form of transcranial electrical stimulation. The rats did not appear to be in pain when the TcES was applied. In a preliminary, unpublished, experiment TcES was applied (50 mA, 300 Hz, 250 μS, biphasic pulses) via concentric ring electrodes and conventional disc electrodes. The rats tolerated the concentric ring electrode TcES well and continued to roam around the cage while TcES was applied. In contrast, when the electrical stimulation was applied via conventional electrodes, the rats had vocalizations, escape behavior, and uncontrollable motor activity. The underlying mechanism that could explain such a contrast in the electrographic and behavioral effects of the two different stimulation techniques is not yet clear, but we suggest that it is related to the spatial distribution of the electrical field caused by stimulation. With the concentric ring electrode stimulation the field effect is vertically concentrated below the center disc, whereas the conventional stimulation causes more parallel distribution of the field effects between both electrodes.

Taken together with previous effects observed in models of status epilepticus induced by pilocarpine (Besio et al., 2007) and penicillin (Besio et al., 2005), these results indicate that the seizure control achieved with noninvasive TcES is applicable to diverse seizure types and mechanisms of seizure induction. These results also suggest that in the future TcES has the potential to be a viable noninvasive therapy for intractable epilepsy.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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