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Research Report

Suppression of acute seizures by theta burst electrical stimulation of the hippocampal commissure using a closed-loop system

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ABSTRACT

This study investigated the effects of electrical stimulation with theta burst stimulation (eTBS) on seizure suppression. Optimal parameters of eTBS were determined through open-loop stimulation experiments and then implemented in a close-loop seizure control system. For the experiments, 4-aminopyridine (4-AP) was injected into the right hippocampus of Sprague–Dawley rats to induce an acute seizure. eTBS was applied on the ventral hippocampal commissure and the effects of eTBS with different combinations of burst frequency and number of pulses per burst were analyzed in terms of seizure suppression. A closed-loop seizure control system was then implemented based on optimal eTBS parameters. The efficiency of the closed-loop eTBS was evaluated and compared to that of high frequency stimulation. The results show that eTBS induced global suppression in the hippocampus and this was sustained even after the application of eTBS. The optimal parameter of eTBS in the open-loop stimulation experiments was a burst frequency at 100 Hz with nine pulses in a burst. The eTBS integrated with the on–off control law yielded less actions and cumulative delivered charge, but induced longer after-effects of seizure suppression compared to continuous high frequency stimulation (cHFS). To conclude, eTBS has suppressive effects on 4-AP induced seizure. A closed-loop eTBS system provides a more effective way of suppressing seizure and requires less effort compared to cHFS. eTBS may be a novel stimulation protocol for effective seizure control.

Abbreviations: eTBS, electrical stimulation with theta burst stimulation protocol; cHFS, continuous high frequency stimulation; postSET, post-stimulation effective time

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1. Introduction

Deep brain stimulation on epileptic foci is an emerging treatment of intractable epilepsy. However, the optimal stimulation paradigm needs to be determined and stimulation parameters are crucial. An early study shows that high frequency stimulation can suppress epileptiform activity in the hippocampal slice (Lian et al., 2003). *In vivo* chemoconvulsant models have shown that electrical high frequency stimulation in the hippocampus is effective in suppressing acute seizures (Chiang et al., 2013b), reducing seizure duration, and increasing inter-spike intervals (Rajdev et al., 2011). Moreover, the results of clinical trials also support the idea that hippocampal stimulation in the high frequency range can reduce seizure frequency by 30–90% (Boon et al., 2007; McLachlan et al., 2010; Tellez-Zenteno et al., 2006).

Another possible treatment for epilepsy is transcranial magnetic stimulation (TMS). Depending on the protocol, TMS facilitates or inhibits synaptic transmission. Repetitive transcranial magnetic stimulation (rTMS) in the frequency range of 5–20 Hz produces long-term potentiation-like excitatory effects for several minutes after stimulation (Pascualleone et al., 1994). On the other hand, rTMS in the low frequency range of 0.9–1 Hz induces long-term depression-like inhibitory effects (Chen et al., 1997; Wassermann et al., 1996). Therefore, 1 Hz rTMS with 1200 pulses can decrease the number of seizures in patients with refractory epilepsy and this suppressive effect can sustain for two months (Fregni et al., 2006). Similarly, 0.5 Hz rTMS with 900 pulses effectively reduces seizure frequency in patients with focal neocortical epilepsy (Santiago-Rodríguez et al., 2008). A recent study has also shown that rTMS can reduce the inter-ictal epileptic discharge frequency and improve the psychological condition of patients with refractory partial epilepsy (Sun et al., 2012). Moreover, rTMS induces the acute effects of modulating epileptiform discharges in patients with frontal lobe epilepsy (Kimiskidis et al., 2013).

Theta burst stimulation (TBS) is a type of TMS with a stimulation pattern containing bursts of 50 Hz pulse train with a burst rate of 5 Hz. Continuous TBS can induce inhibitory effects that last for many minutes (Huang et al., 2005). Compared to low frequency TMS, TBS causes longer inhibition and requires lower stimulation intensity (Cárdenas-Morales et al., 2010).

Although TBS is a protocol originally created for magnetic stimulation, the waveform can be implemented for electrical stimulation and could have similar effects. More details of the rationales are described as follows. First of all, both electrical and magnetic stimulations in the low frequency range can suppress seizures, they may share some similar inhibitory mechanisms. Second, the TBS paradigm can induce inhibitory effects, and thus electrical stimulation with the TBS protocol may have an potentially suppressive effect on seizures. Finally, TBS combines both high and low frequency stimulations and then may provide the benefits of both kinds of electrical stimulation for seizure control.

After the paradigm is determined, another decision to be made is the stimulation target. The fiber tract is a recent choice of stimulation location while the tract stimulation can affect large region of the brain and increase the spatial extent of effects. Low frequency stimulation in the ventral hippocampal commissure reduces seizure frequency in the chronic animal model of temporal lobe epilepsy (Rashid et al., 2012). Similarly, high frequency stimulation in the same region suppresses 4-aminopyridine (4-AP)-induced seizures (Chiang et al., 2013b). Low frequency stimulation of the fornix also reduces epileptiform discharges and seizures in patients with intractable mesial temporal lobe epilepsy (Koubeissi et al., 2013).

Therefore, this study investigated the effects on seizure suppression by electrical stimulation with TBS protocol (eTBS) in the ventral hippocampal commissure. Following open-loop stimulation experiments to establish optimal parameters of eTBS, the parameters were implemented in a close-loop seizure control system.

2. Results

2.1. Seizure suppression by eTBS

The characteristics of 4-AP induced seizures were described in a previous study (Chiang et al., 2013b). In the present study, eTBS could cause global suppression and post-stimulation suppression effects in the hippocampus. Furthermore, seizure suppression was an all-or-none effect. To clearly identify the effects of stimulation, the stimulation artifacts were removed in advance by means of an algorithm developed in a previous study (Chiang et al., 2013b). When eTBS was applied for 2 s, global seizure suppression occurred not only during the period of stimulation but also for a while after the stimulation (Fig. 1). The partial suppression, which meant that suppression only occurred in some regions of the hippocampus, was also observed. However, partial suppression was classified as a failure case of suppression in this study. Moreover, since post-stimulation suppressive effects happened in six regions of the hippocampus, the minimum

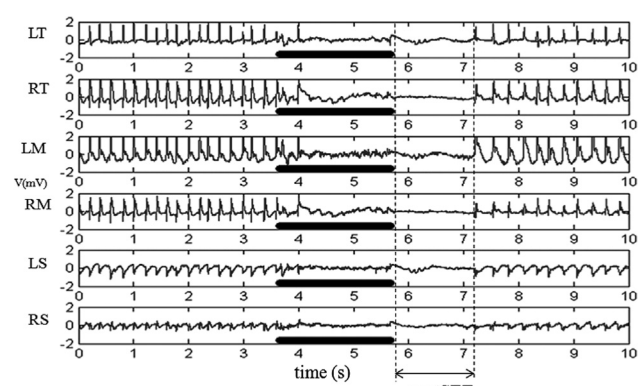

Fig. 1 – An example of seizure suppression by eTBS in the left septal (LS), right septal (RS), left median (LM), right median (RM), left temporal (LT), and right temporal (RT) CA1 regions of the hippocampus. Seizures were suppressed globally and the suppression effects persisted during post-stimulation effective time (postSET). The bold line was the period of eTBS application.