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Low-frequency Electric Cortical Stimulation Has an Inhibitory Effect on Epileptic Focus in Mesial Temporal Lobe Epilepsy

*Junichi Yamamoto, †Akio Ikeda, ‡Takeshi Satow, *Kazuhide Takeshita, ‡Motohiro Takayama, *Masao Matsuhashi, *Riki Matsumoto, *Shinji Ohara, ‡Nobuhiro Mikuni, ‡Jun Takahashi, ‡Susumu Miyamoto, §Waro Taki, ‡Nobuo Hashimoto, *John C. Rothwell, and *†Hiroshi Shibasaki

**Human Brain Research Center, Departments of †Neurology and ‡Neurosurgery, Kyoto University Graduate School of Medicine, Shogoin, Sakyo, Kyoto; and §Department of Neurosurgery, Mie University School of Medicine, Edobashi, Tsu, Mie, Japan*

Summary: *Purpose:* This study was conducted to investigate the effect of low-frequency electric cortical stimulation on epileptic focus in humans.

Methods: We stimulated the epileptic focus in a patient with medically intractable mesial temporal lobe epilepsy (MTLE) by means of subdural electrodes and evaluated the change in the number of interictal epileptiform discharges. We used biphasic electric current of 0.3-ms duration presented at 0.9-Hz frequency for 250 s, comparing stimulus intensity of 7.5, 2, and 0.5 mA.

Results: Interictal epileptiform discharges at the ictal focus occurred less frequently after the stimulation with the intensity of 0.5 mA. With the intensity of 7.5 mA and 2.0 mA, however, habitual auras were elicited by the stimulation, and afterdischarges were seen on the cortical EEG.

Conclusions: Low-frequency, low-intensity electric cortical stimulation could produce inhibitory effects on epileptic activity. At the same time, however, a caution for possible induction of EEG seizures is needed, even when applying low-frequency electric stimulation. **Key Words:** Low-frequency electric cortical stimulation—Subdural electrode—Intractable epilepsy—Interictal epileptiform discharge—Inhibitory effects.

Low-frequency repetitive transcranial magnetic stimulation (rTMS) was reported to have an inhibitory effect on epileptic activity in patients with medically intractable complex partial seizures (1,2). Low-frequency electric stimulation also was shown to have an inhibitory effect on the epileptic foci in kindling rats (3). We had an opportunity to deliver electric stimulus directly to the epileptic focus in a patient with medically intractable mesial temporal lobe epilepsy (MTLE) to evaluate whether it could suppress the epileptic activity. In this study, we investigated the inhibitory mechanism of low-frequency stimulation through subdural electrodes, which can apply an effect to a more restricted cortical area as compared with TMS. An abstract form of this study was published elsewhere (4).

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Address correspondence and reprint requests to Dr. H. Shibasaki at Human Brain Research Center and Department of Neurology, Kyoto University Graduate School of Medicine, Shogoin, Sakyo, Kyoto, 606-8507, Japan. E-mail: shib@kuhp.kyoto-u.ac.jp

PATIENTS AND METHODS

A 31-year-old man was referred to our hospital because of medically intractable complex partial seizures. His medical history was not remarkable except for a vacuum extraction at birth and febrile convulsions at age 2 years. At age 3 years, he began to have complex partial seizures. Each seizure started with an epigastric rising sensation followed by loss of consciousness and oral automatism. His seizures were not controlled completely, even with various combinations of phenytoin (PHT), phenobarbital (PB), zonisamide (ZNS), valproic acid (VPA), and so on. The seizues occurred with an average frequency of 1 to 3 times per month, with the longest seizure-free interval of 1 month. The maximal seizure frequency was 1 to 2 times per day.

At age 30 years, he had an intensive workup for his epilepsy as follows. A head magnetic resonance imaging (MRI) showed left hippocampal atrophy and a streak lesion in the base of the left posterior temporal region (Fig.1). Interictal ^{18}fluorodeoxyglucose–positron emission tomography (FDG-PET) showed a hypometabolic area in the left temporal region. Interictal epileptiform

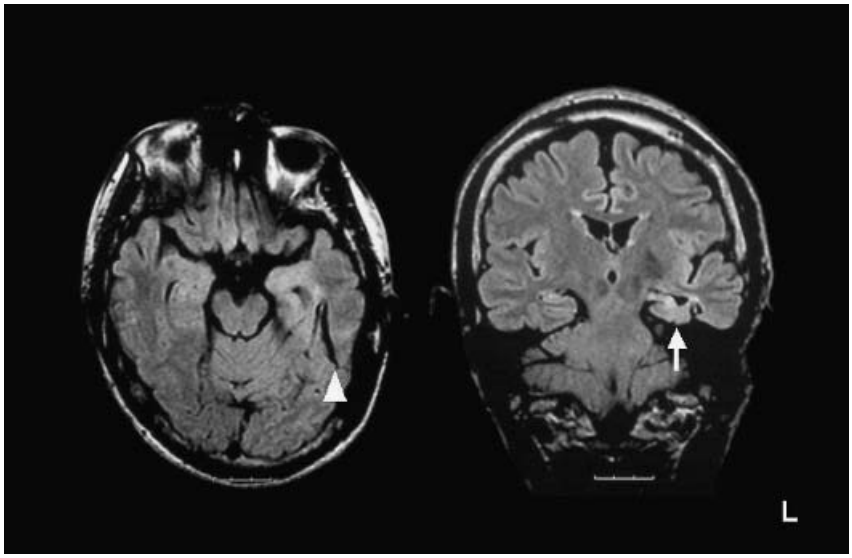

FIG. 1. Head magnetic resonance imaging scan of this patient showing the left hippocampal atrophy (arrow) and a streak cavity in the left mid-to-posterior temporal region (arrowhead).

discharges were seen exclusively at the left anterior temporal region 10 to 20 times per night.

During the long-term video-EEG monitoring, six habitual seizures were recorded, all of which showed a common ictal EEG pattern starting from T1 electrode. They spread rapidly to bilateral occipital areas, clinically associated with blurred vision. Intracarotid amobarbital test showed that his language and memory functions were both represented exclusively in the left hemisphere. Thus it was most likely that the patient had left MTLE, but we could not exclude the possibility that a small streak lesion in the left posterior temporal region just posterior to the hippocampus also was responsible for the seizure generation.

Therefore the patient underwent implantation of subdural electrodes for further analysis of the ictal-onset zone before surgical treatment. Informed consent was obtained from the patient after the purpose, and the possible consequence of invasive monitoring was explained, in accordance with the Clinical Protocol No. 79 approved by the Ethical Committee of Kyoto University Graduate School of Medicine. Three subdural grid electrodes, 2 × 8(A), 4 × 5(B), and 1 × 6(C), each electrode with 3 mm diameter and center-to-center interelectrode distance of 1 cm (AD-TECH Co.), were permanently implanted on the left temporal lobe, as shown in Fig. 2a. Interictal spikes were most frequently seen at electrode A1 and A9 (Fig. 2b), from which EEG seizure patterns started. In addition to the left medial temporal region, the habitual seizures also started from around the streak cavity in the left posterior temporal region. The patient had 14 clinical seizures during the invasive monitoring, some of which started at two or more electrodes. Of the 14 seizures, three started from the electrode A9, two each from the area formed of A2, A3, A9, and A10; that of A2, A3, A9, A10, and C1; and that of A2, A9, A10, C1 and C2, and one each from the area formed of A1 and A9; that of A1, A2, A9, and A10; that of A9, A10, C1, and C2; that of C1 and C2; and C3. Repetitive 50-Hz electric stimulation of 1- to 5-s duration was given to each electrode for the purpose of cortical mapping by using the method previously described (5).

The patient gave another informed consent for this specific study in accordance with the Clinical Research Protocol No. 235 approved by the Ethical Committee of Kyoto University Graduate School of Medicine. Stimulation trials were performed while the patient was seated on a reclining bed comfortably with his eyes open and awake. A1 and A9 electrodes were stimulated bipolarly. At first we used 0.3-ms square pulses of alternating polarity presented at 0.9 Hz, and the intensity was set to 7.5 mA. Each stimulus session lasted 250 s, and five sessions were given. The number of interictal epileptiform discharges was counted for the 5-min period before the first session and between each consecutive session, and for two 5-min periods after the fifth session. We could not count the number of interictal epileptiform discharges during the stimulation because of the stimulus artifacts.

For the control study, taking into account that the number of interictal epileptiform discharges could change spontaneously, we counted the number of interictal epileptiform discharges without stimulation on two different occasions while the patient was awake. In this study, interictal epileptiform discharge was defined as a transient and clearly outstanding activity from the background with a pointed peak and duration of 20–200 ms followed by a slow wave. According to these criteria, two investigators (K.T. and T.S.) independently counted the number of interictal epileptiform discharges in the EEG materials printed on paper without any information about recording conditions (i.e., control, before stimulation, or after stimulation). The numbers of spikes

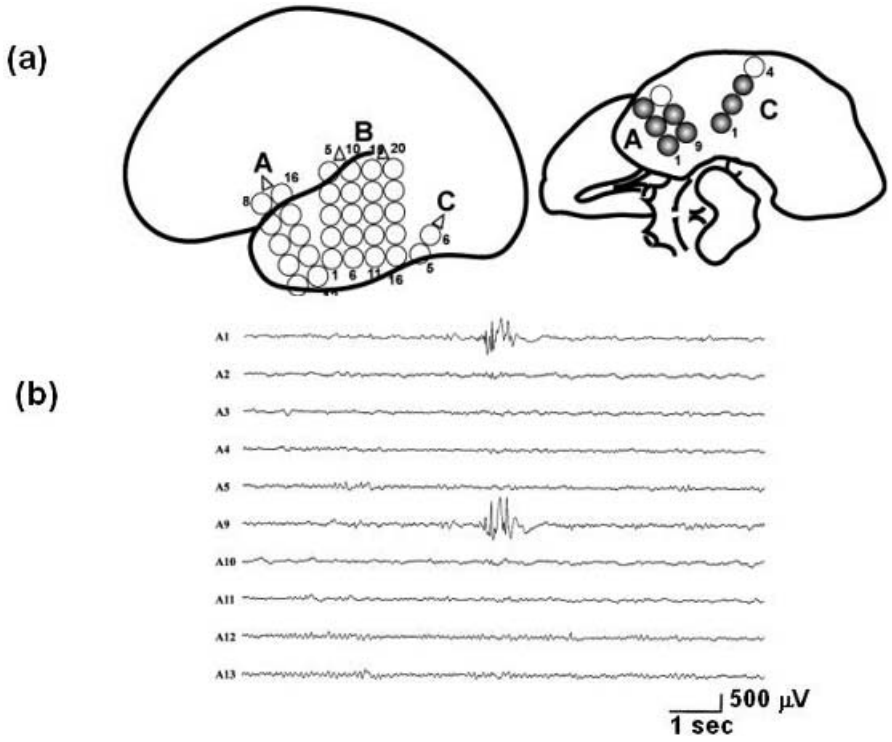

FIG. 2. Electrode placement and interictal epileptiform discharges. **A:** Three subdural electrode grids or strips (A, B, and C) were implanted. In 14 recorded seizures, ictal EEG patterns started at either one of the electrodes A1, A2, A3, A9, A10, C1, C2 and C3, or in various combination of these (solid circle). **B:** Interictal spikes were seen most frequently at A1 and A9.

counted by the two investigators were averaged for final output.

RESULTS

Immediately after starting stimulation of the electrodes A1 and A9 with the intensity of 7.5 mA, the patient developed a habitual aura associated with EEG seizure pattern, and this aura disappeared as soon as the stimulation was discontinued. The patient developed the same habitual aura with the same EEG seizure pattern also with the intensity of 2 mA (Fig. 3). Therefore we used the intensity of 0.5 mA on a different day, which did not elicit an aura. The number of interictal epileptiform discharges decreased after the second stimulus session, and the minimal spike count was reached after the third session (Fig. 4). The number of interictal epileptiform discharges began to increase after the fourth session, but did not reach the prestimulus level. Under the control condition (no stimulation), the number of interictal epileptiform discharges spontaneously fluctuated, but no consistent pattern was seen (Fig.5).

The patient underwent left tailored temporal lobectomy after we defined the Seizure-onset zone at the elec-

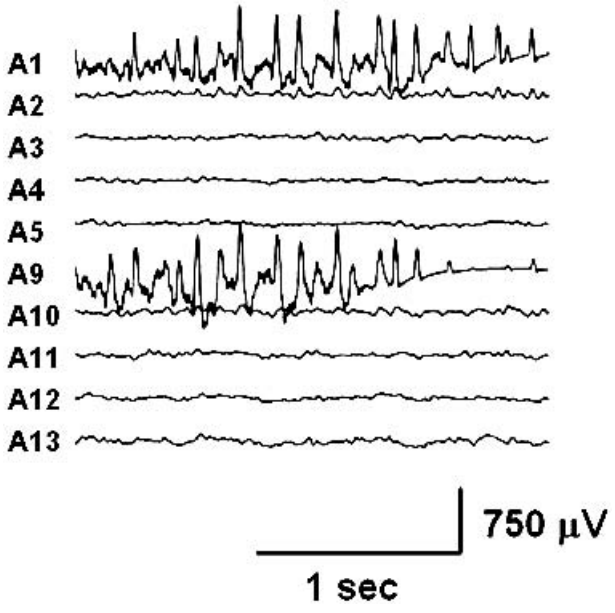

FIG. 3. Effect of electric cortical stimulation. Afterdischarges were induced by 0.9-Hz low-frequency electric cortical stimulation of electrodes A1 and A9 with an intensity of 2.0 mA.

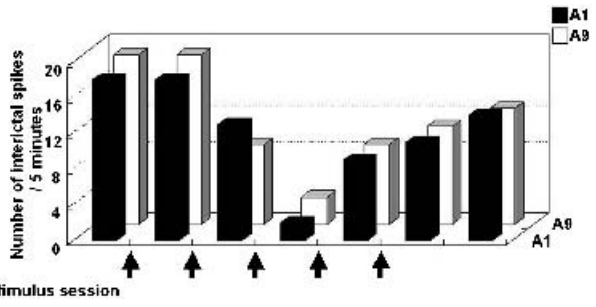

FIG. 4. Changes of interictal epileptiform discharges at electrodes A1 and A9 through five consecutive sessions of electric stimulation at 0.9 Hz. Interictal epileptiform discharges occurred least frequently after the third stimulus session.

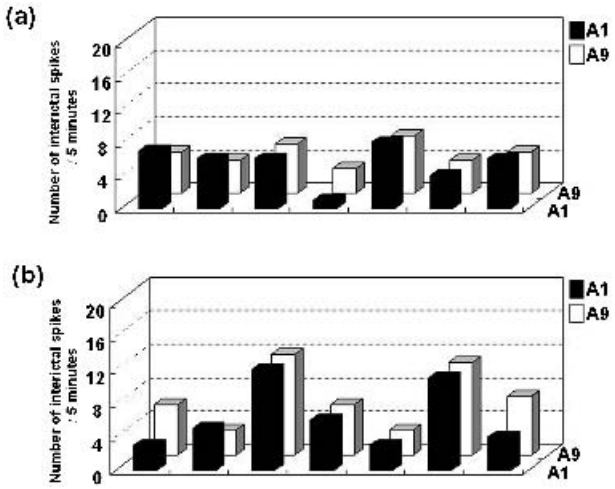

FIG. 5. Spontaneous changes of interictal epileptiform discharges counted at electrodes A1 and A9 on seven occasions each for 5 min with an interval of 250 s in no-stimulus control condition. Samples were taken from two different occasions **(A, B).** Note that spike frequency does not change systematically.

trode A1 and A9 and after we identified the functional cortical area. He had no seizures during the observation period of 10 months after surgery.

DISCUSSION

These results showed that 0.9-Hz electric stimulation directly applied to the epileptic focus produced both inhibitory and excitatory effects on the epileptic activity, depending on the stimulus intensity. Inhibitory effect was obtained by using a stimulus intensity as low as 0.5 mA, whereas the excitatory effect was produced by using much stronger stimuli (7.5 and 2.0 mA). Several previous studies have shown that low-frequency rTMS has an inhibitory effect on cortical excitability (6–10) and on epileptic focus (1,2) in humans. Chen et al. (6) raised a caution even with low-frequency rTMS, because it might cause the spread of excitation to cause seizures. They showed that low-frequency rTMS could produce not only inhibitory but also excitatory effects on the human motor cortex.

Because we used subdurally placed electrodes of 3 mm diameter for stimulation, it is most likely that a much smaller cortical area was activated as compared with TMS. In addition, because we stimulated the epileptic focus directly by using subdural electrodes, the risk of seizure induction even by low-frequency stimulation would be higher if it produced only excitatory effects. For producing inhibitory effects, optimal stimulus conditions for low-frequency stimulation to the epileptic focus may not be the same as those for rTMS. We have to consider the optimal stimulus conditions in each patient, including not only the frequency but also the intensity and duration of each pulse.

In electric current stimulation, anodal stimulus can activate the majority of pyramidal neurons directly, because an anode on the surface of the cortex produces electric current that can flow into the vertically oriented dendrites of pyramidal neurons and then excite or depolarize the initial segment region or the first node of the axon. Cathodal electric stimulation, conversely, can excite neurons in the outer cortical layer, which indirectly excites pyramidal cells, just as in the case in TMS (11). This interpretation for electric brain stimulation is applicable not only for the scalp stimulation but also for the direct cortical stimulation. Conversely, when a magnetic coil stimulator is placed on the scalp, it is speculated that the rapid change in magnetic field readily induces an electric current in the brain parallel to the scalp surface, but no current flow perpendicular to the surface. It could depolarize the horizontal interneurons or afferent fibers, which might then excite pyramidal tract cells transsynaptically (12). Because we used alternating 0.9-Hz electric stimuli between the two adjacent subdural electrodes, the major electric current could be parallel to the cortical surface, and thus it would produce the similar situation to TMS, although the current direction changed every 1.1 s.

In the present case, 0.9-Hz electric cortical stimulation for 250 s was applied 5 times with the interval of 5 min. Interictal epileptiform discharges occurred least frequently after the third stimulus session. Although the number of interictal epileptiform discharges increased after the fourth session, they did not return to the baseline level. Low-frequency rTMS at 1 Hz applied to the human motor and visual cortices for 15 min has been shown to produce inhibitory effects lasting $\geq$15 and 10 min, respectively (6,7). Considering apparently transient inhibitory effects, the stimulation for 250 s used in the present study may not be long enough to obtain a longer inhibitory effect lasting >10 min.

Long-term depression (LTD) induced by low-frequency electric stimulation in the hippocampus (13), visual cortex (14), and motor cortex (15) is thought to be one of the main mechanisms underlying the inhibitory effects. Although LTD may be a major possible mechanism to explain the effect of low-frequency stimulation, LTD alone may not explain both the excitatory and inhibitory effects, which depend on the intensity applied to the epileptic foci in this patient.

Weiss et al. (3) reported that 1-Hz electric stimulation of the kindled amygdala for 15 min produced inhibitory effects on the epileptic activity in rat. Velasco et al. (16) also showed that electric stimulation of the hippocampus delivered as biphasic Lilly wave pulses with 130 Hz in frequency, 0.45 ms in duration, and 0.2–0.4 mA in amplitude for 23 h/day for 2–3 weeks could suppress temporal lobe epileptogenesis in humans. These two studies indicate that both low- and high-frequency electric stimulation directly applied to the epileptic foci can pro-

duce antiepileptic effects. The present report is the first to show that low-frequency (0.9 Hz) electric stimulation directly applied to the epileptic focus can produce the inhibitory effects in humans.

Although the present result was obtained from a single patient, we postulate that low-frequency electric cortical stimulation with optimal intensity could produce an inhibitory effect on the epileptic foci.

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