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Repetitive transcranial magnetic stimulation decreases the kindling induced synaptic potentiation: Effects of frequency and coil shape

Ali Yadollahpour[a], **Seyed Mohammad Firouzabadi**[a], **Marzieh Shahpari**[b], **Javad Mirnajafi-Zadeh**[b,*]

[a] *Department of Medical Physics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran*
[b] *Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran*

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Summary The present study was aimed to investigate the effects of repetitive transcranial magnetic stimulation (rTMS) on kindling-induced synaptic potentiation and to study the effect of frequency and coil shape on rTMS effectiveness. Seizures were induced in rats by perforant path stimulation in a rapid kindling manner (12 stimulations/day). rTMS was applied at different frequencies (0.5, 1 and 2 Hz), using either figure-8 shaped or circular coils at different times (during or before kindling stimulations). rTMS had antiepileptogenic effect at all frequencies and imposed inhibitory effects on enhancement of population excitatory postsynaptic potential slope and population spike amplitude when applied during kindling acquisition. Furthermore, it prevented the kindling-induced changes in paired pulse indices. The inhibitory effect of rTMS was higher at the frequency of 1 Hz compared to 0.5 and 2 Hz. Application of rTMS 1 Hz by circular coil imposed a weaker inhibitory action compared with the figure-8 coil. In addition, the results showed that pretreatment of animals by both coils had similar preventing effect on kindling acquisition as well as kindling-induced synaptic potentiation. Obtained results demonstrated that the antiepileptogenic effect of low frequency rTMS is accompanied with the preventing of the kindling induced potentiation. This effect is dependent on rTMS frequency and slightly on coil-type.

* Corresponding author at: Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, PO Box: 14115-331, Tehran, Iran. Tel.: +98 21 82883865; fax: +98 21 82884555.
E-mail addresses: mirnajaf@modares.ac.ir, javad.mirnajafi@google.com (J. Mirnajafi-Zadeh).

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Introduction

Epilepsy is a chronic neurological disorder which is characterized by sudden and recurrent seizures (Chang and Lowenstein, 2003). Seizures are a consequence of changes in neuronal membrane excitability (Kullmann, 2002) accompanied with the hyperexcitability of the cortical areas (Tassinari et al., 2003; Cantello et al., 2007). Although drug therapy is the most commonly used for treatment of epilepsy, however, some epileptic patients are resistant to anticonvulsant drugs. Repetitive transcranial magnetic stimulation (rTMS) has recently gained considerable research attention as a new therapeutic approach in drug-resistant epilepsies for its non-invasive and easily applied technology. It has been suggested that effects of rTMS are due to the rTMS-induced modulation of cortical excitability (Fitzgerald et al., 2006).

Despite the conflicting findings of previous studies, there are a lot of evidence indicating the efficacy of low-frequency (<5 Hz) rTMS in reducing the occurrence of seizure and interictal epileptiform discharges in epileptic patients (Kotova and Vorob'eva, 2007) and experimental models of epilepsy including kindling (Anschel et al., 2003).

Among different rTMS parameters, frequency, duration, time of application and the coil shape play critical roles in its effectiveness (Godlevsky et al., 2006; Rotenberg et al., 2008; Huang et al., 2009). Many of these parameters such as frequency and time of application are also important in induction of depotentiation and long-term depression (LTD) by electrical low-frequency stimulation (Martin, 1998; Kemp et al., 2000; Straube and Frey, 2003; Huang et al., 2009). On the other hand, the mechanisms involved in depotentiation may have a role in the anticonvulsant effects of rTMS (Chen et al., 1997). It means that application of rTMS may prevent the kindling-induced changes in synaptic transmission.

It has been suggested that kindling stimulations induce a special kind of long-term enhancement of excitatory post synaptic potentiation (EPSP), named kindling-induced potentiation (Gilbert and Mack, 1990; Cain et al., 1992). This type of potentiation is similar, but not the same as, long-term potentiation (Cain et al., 1992). Kindling-induced potentiation is believed to exert an essential role in the progression of kindling. Application of electrical low-frequency stimulations, which has inhibitory effect on kindling-induced potentiation, is accompanied with antiepileptogenic effects (Mohammad-Zadeh et al., 2007). Therefore, it is valuable to study the effect of rTMS on synaptic potentiation during kindling acquisition. On the other hand, the rTMS patterns exerting the best antiepileptogenic effect may also exert more inhibitory effect on kindling-induced synaptic potentiation.

Therefore, the present study was aimed to investigate the therapeutic and preventive effects of rTMS in perforant path kindling through evaluating the changes in kindling-induced synaptic potentiation in rat. The antiepileptogenic effect of rTMS was assessed through its application during kindling acquisition and the preventive effect of rTMS was studied by its application before the kindling stimulations. Furthermore, we evaluated the impacts of the frequency and coil shape as two important parameters of rTMS on its anticonvulsant effects.

Materials and methods

Animals

Adult male Wistar rats (weighing 280—300 g at the time of surgery) were obtained from Pasteur Institute of Iran (Tehran, Iran). Animals were kept in a colony room with a constant temperature (25 ± 2 °C), humidity (50 ± 5%) and artificial 12:12-h light—dark cycle in individual cages with wood-chip bedding and had free access to standard food and water. All studies were performed in accordance with the ethical guidelines set by the ''Ethical Committee of Faculty of Medical Sciences, Tarbiat Modares University'', which completely coincide with the 'National Institutes of Health Guide for the Care and Use of Laboratory Animals'. All experiments were conducted during the same time of day (10:00 AM to 6:00 PM).

Surgical procedure

Under ketamine/xylazine (100/10 mg/kg, i.p.) anesthesia, animals underwent stereotaxic implantation of a twisted bipolar stimulating electrode with a tip distance of 0.5 mm in the perforant path (coordinates: AP, −6.9 mm; L, 4.1 mm; and V, 2.0—2.5 mm below dura) and a monopolar recording electrode in the dentate gyrus (coordinates: AP, −2.8 mm; L, 1.8 mm; and V, 2.5—3.0 mm below dura) of the right hemisphere (Paxinos and Watson, 1986). The incisor bar was set 3.3 mm below the interaural line. The depth of the recording and stimulating electrodes was adjusted to yield maximum population spike (PS) amplitude in the dentate gyrus in response to perforant path stimulation. Electrodes were stainless steel, teflon-coated, 127 μm in diameter, and insulated except at their tips (A-M Systems, WA, USA).

Two other electrodes were connected to stainless steel screws and located above the frontal and occipital cortices as reference and ground electrodes. All electrodes were connected to pins of a lightweight multichannel miniature socket as a head-stage and fixed to the skull with dental acrylic.

Rapid kindling procedure

Following a 10-day recovery period, rats were transferred from the home cage to a recording box. The head-stage of the rat was connected to a flexible and shielded cable. Afterdischarge (AD) threshold was determined by 1 ms monophasic square wave of 50 Hz with 3 s train duration as described previously (Mohammad-Zadeh et al., 2007; Sadegh et al., 2007). The stimulating currents were initially delivered at 10 μA and then its intensity was increased in increments of 10 μA at 5 min intervals. The minimum intensity sufficient to induce the ADs for at least 8 s was selected as the AD threshold and used for kindling stimulation. The AD was defined as spikes with a frequency of at least 1 Hz and amplitude of at least twice the baseline activity originating immediately post stimulation. In this study, the AD threshold intensity of different animals ranged from 20 to 150 μA. Rats were electrically stimulated at the AD threshold 12 times a