Review

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Clinical Application of TMS to Epilepsy

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The role of transcranial magnetic stimulation in epileptology is discussed in this article. Usefulness of TMS are discussed as a diagnostic tool in testing altered cortical excitability in patients with epilepsy and the modes of action of antiepileptic drugs, which are helpful to evaluate the pathophysiology of epilepsy. Also potential therapeutic tool in epilepsy with repetitive transcranial magnetic stimulation would be mentioned. **(2012;2:25-28)**

Key words: Transcranial magnetic stimulation; Epilepsy; Cortical excitability; Antiepileptic drugs; Repetitive TMS

Although more than ten new antiepileptic drugs have been developed and used for epilepsy patients who are resistant to conventional antiepileptic medications, 20-30% of patients still are having difficulty in controlling their epileptic seizures. For intractable epilepsy patients, recently, cerebellar, thalamic, hippocampal, and vagal nerve stimulation have been used for the treatment of epilepsy.[1,2] All involve surgical procedures, and only vagal stimulation is an approved therapy. Transcranial magnetic stimulation (TMS), used extensively in clinical neurophysiology, is an alternative approach. Whereas high-frequency stimulation increases motor cortex excitability and rarely has led to seizures in experimental subjects, low-frequency stimulation reduces cortical excitability.[3,4] A number of preclinical studies have attempted to model the potential effects of brain stimulation on cortical excitability; in most but not all studies, low-frequency electrical stimulation, delivered via intracranial electrodes, has been inhibitory and high frequency facilitatory.[5-7] Recently, 0.5-Hz TMS increased the latency to pentylenetetrazole-induced seizures in Wistar rats.[8] In 1980, Merton and Morton first reported successful motor cortex stimulation in an unanesthetized human with strong electric shocks delivered through the intact skull.[9] Although noninvasive, transcranial electric stimulation is painful because of activation of pain fibers in the scalp. Barker *et al*. showed that painless transcranial stimulation of the human brain could be performed using the small electric field induced by a time-varying magnetic field, which in turn is produced by passing a large current through an insulated copper-wire coil placed above the scalp.[10] As the magnetic field is virtually unattenuated by the scalp and skull, the induced electric current could activate superficial neural elements.[11] TMS was first used to study corticospinal motor conduction. However, it became more and more evident that TMS also provided a noninvasive evaluation of distinct excitatory and inhibitory functions of the human cerebral cortex.[12-15] Epileptic conditions are characterized by heterogeneous and dynamic pathophysiological processes leading to an altered balance between excitatory and inhibitory influences at the cortical level.[16] Antiepileptic drugs (AED) work by counteracting such imbalance with different mechanisms.[17] Therefore, TMS has been regarded as a promising tool to assess noninvasively pathophysiological mechanisms and effects of AEDs in patients with epilepsy. However all TMS studies published previously were performed on healthy subjects. Therefore, none of the observed AED effects can be ascribed brain pathology. However, the observed AED effects might have affected the TMS measures in patients with epilepsy when treated with AED. In all studies, similar protocol was used. Motor excitability was measured immediately before the administration of a single AED dose (baseline). Thereafter, repeat measurements were performed at delays adjusted to the pharmacokinetics of the individual AED. The basic concept of previous studies is that AED with different modes of actions may produce different patterns of effects on the various TMS measures of motor excitability. It may be possible to define patterns of effects for AED whose modes of action are unknown. Among new AED, zonisamide (ZNS) effect on cortical excitability was studied for the first time in our laboratory. We enrolled 15 drug-naïve idiopathic generalized epilepsy (IGE) patients (8 male, mean age 24.9 yrs). The

TMS parameters obtained using two Magstim 200 stimulators were; resting motor threshold (RMT), motor evoked potential (MEP) amplitudes, cortical silent period (CSP), short intracortical inhibition (SICI), and intracortical facilitation (ICF). TMS parameters were compared before and after ZNS administration. All patients were administered ZNS monotherapy (200 mg/day) for 8 weeks. No patient reported seizures during the study period. After ZNS treatment MEP amplitudes were significantly reduced in right (-34.2%) and left hemispheres (-37.0%) (Wilcoxon's signed rank test after Bonferroni's correction for multiple comparisons, $p<0.05$). Mean RMT, CSP, and SICI/ICF were not changed by ZNS ($p>0.05$). These our findings suggest that ZNS decreases cortical excitability in patients with IGE and MEP amplitudes are useful TMS parameters for evaluating changes in cortical excitability induced by ZNS. The findings in this study are helpful to understand how ZNS affects the excitability of the motor cortex in patients with IGE.[18]

Later, TMS study after ZNS was performed in focal epilepsy (FE) patients to compare the different aspect of AED effect on cortical excitability between IGE and FE patients.[19] All 24 patients were treated with ZNS monotherapy (200-300 mg/day) for 8-12 weeks. After ZNS, MEP amplitudes decreased (-36.9%) significantly in epileptic hemispheres (paired *t*-test with Bonferroni's correction for multiple comparisons, $p<0.05$) (Figure 1), whereas the mean RMT, CSP, SICI, and ICF were unchanged ($p>0.05$). ZNS did not affect cortical excitability in nonepileptic hemispheres. These findings suggest that ZNS decreases cortical excitability only in the epileptic hemispheres of focal epilepsy patients. MEP amplitudes may be useful for evaluating ZNS-induced changes in cortical excitability and also TMS findings may be helpful to differentiate IGE from FE by changes of cortical excitability.

It is well known that the excitability of cortical networks can be modulated by trains of regularly repeated magnetic stimuli.[20-22] Hence, repetitive TMS (rTMS) could even have therapeutic potential in epileptic patients. The effects of rTMS on the excitability of cortical networks depend on its frequency, intensity, and duration and on the intertrain intervals.[22,23] During trains of rTMS, corticospinal excitability can be monitored by recording the EMG responses from different muscles. Moreover, ICI was reduced and ICF was increased for minutes after each train,[24] whereas the size of MEPs following TES was unchanged.[25] These data indicate that, in normal subjects, high-frequency suprathreshold rTMS can produce an enhancement in M1 excitability (i.e. in the balance between cortical excitatory and inhibitory phenomena) that outlasts the application of the train. In contrast, both excitatory and inhibitory effects on M1 have been reported after high-frequency rTMS trains delivered at (or below) RMT intensity.[26-28] It has been suggested that inhibition and facilitation could predominate according to the train duration[29] and the stimulus frequency.[26]

In normal subjects, application of low-frequency trains of rTMS produces a relatively long-lasting suppression of cortical excitability. In addition, 0.5 Hz rTMS prolonged the latency for development of pentylenetetrazol-induced seizures in rats.[8] These data provide a rationale for using low-frequency rTMS to treat patients affected by epilepsy and epileptic myoclonus. In an open pilot study,[30] investigated the effects of 0.33 Hz rTMS delivered on 5 consecutive days in 9 patients with drug-resistant FE (two temporal, 7 extratemporal). Each day, two trains of 500 pulses at 100% of the RMT were applied by means of a large circular coil placed over the vertex. During the follow-up period (4 weeks before and 4 weeks after the rTMS application) the AED treatment was kept constant. In the post-intervention period, seizure frequency was significantly reduced compared with the pre-intervention period. In a patient with intractable partial seizures due to a focal cortical dysplasia in the left parasagittal parietal region,[31] used 0.5 Hz trains of 100 subthreshold magnetic stimuli twice a week for 4 consecutive weeks. rTMS was

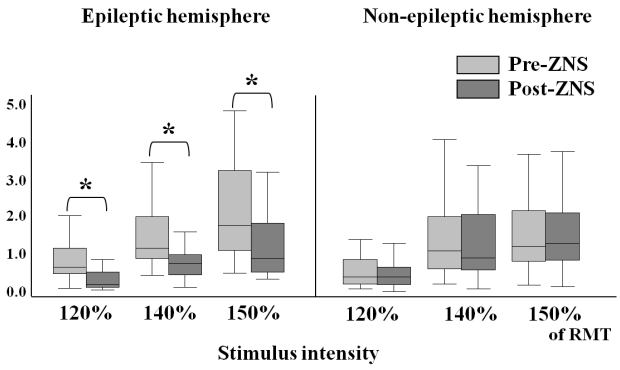

Figure 1. Changes in motor evoked potential (MEP) amplitudes after zonisamide (ZNS) administration in epilepsy patients. After ZNS treatment, MEP amplitudes were significantly reduced at 120%, 140%, and 150% of the resting motor threshold (RMT) stimulation only in epileptic hemispheres. *Paired *t*-test after applying Bonferroni's correction for multiple comparisons ($p<0.05$). Data are presented as medians (horizontal lines through the boxes) with the first and third quartiles (lower and upper lines, respectively) and the smallest and largest values (whiskers extending from the ends of the boxes). Pre-ZNS, before ZNS administration; Post-ZNS, after the ZNS administration. Reprinted from JCN; vol.6; Joo EY, Kim HJ, Lim YH, Ji KW, Hong SB. ''Zonisamide Changes Unilateral Cortical Excitability in Focal Epilepsy Patients''; pp. 189-195; Copyright 2010, with permission from Korean Neurological Association.

delivered by a round coil. During the month of observation, the seizure frequency and the interictal spikes were reduced by 70% and 77%, respectively. These effects of 0.3-0.5 Hz rTMS on seizure frequency have yet to be replicated in randomized blinded trials. In contrast, a controlled study was recently performed to assess the therapeutic potential of 1 Hz rTMS.[32] Twenty-four PE patients were randomized to blinded active or placebo stimulation delivered for 15 min twice daily for 1 week. Active stimulation was administered at 120% of MT using a figure-of-eight coil placed over the EEG focus. For the 'placebo' stimulation, the coil was angled at 90 degrees away from the scalp. A trend toward a short-term reduction of seizure frequency was observed in the active group, whereas placebo stimulation had no effect. However, this difference was not significant. These findings do not necessarily indicate that the seizure reduction observed in the previous reports was merely due to observer expectations and placebo effects. For instance, distinct effects of different rTMS frequencies (0.3-0.5 vs. 1 Hz) could also explain this discrepancy. A preliminary report suggested that low-frequency rTMS could reduce epileptic cortical myoclonus.[33] However the same group performed a sham-controlled study of a larger case series and found no significant beneficial effect with 10 days of 1 Hz rTMS of the motor cortex.[21] Finally, in a patient with drug-resistant epilepsia partialis continua, 15 min long trains of 1 Hz rTMS were delivered daily over the EEG focus at threshold intensity. After 1 week of rTMS, a marked reduction of the frequency of the myoclonic jerks was observed for 30 min after the train completion. Recently we enrolled 35 patients with localization-related epilepsy who had experienced at least one complex partial seizure or a secondarily generalized seizure per week on a constant AED regimen over an 8-week period.[34] rTMS was administered using a Rapid^2 magnetic stimulator with an air-cooled coil at 0.5Hz for 5 consecutive days at 100% of rMT. Patients were divided into a focal stimulation group with a localized epileptic focus, or a non-focal stimulation group with a non-localized or multifocal epileptic focus. These two groups were then randomly subdivided into four subgroups depending on the total number of stimulations administered, i.e., 3000 pulse and 1500 pulse subgroups. Weekly seizure frequencies were determined for 8 weeks before and after rTMS. To compare the number of interictal spikes before and after rTMS, EEG was recorded twice before (1st day) and after rTMS (5th day). Mean weekly seizure frequency was non-significantly decreased after rTMS (8.4→6.8/week, -13.9%), but longer stimulation subgroups (3,000 pulses, -23.0%) tended to have fewer seizures than shorter stimulation subgroups (1,500 pulses, -3.0%), without statistical significance and TMS stimulation site and structural brain lesions did not influence seizure outcome. However, interictal spikes significantly decreased (-54.9%, p=0.012) after rTMS and they totally disappeared in 6 patients (17.1%, 6/35). Our findings showed that low-frequency rTMS reduced interictal spikes, but its effect on seizure outcome was not significant. Focal stimulation for a longer duration tended to further reduce seizure frequency. Also these findings may help clinicians to further investigate the therapeutic potential of the rTMS for patients with intractable epilepsy.

Conclusions

Single-pulse and paired-pulse TMS can detect abnormalities of motor excitability in patients with epilepsy and is useful in delineating specific AED effects in healthy subjects as well as in epilepsy patients. Low-frequency repetitive TMS may be useful for treatment of intractable seizures and for abolishment of interictal epileptiform discharges. Moreover, single-pulse TMS and rTMS can be considered safe for testing and treating patients with epilepsy.

References

1. Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. *Neurology* 1995;45:224-30.
2. Velasco M, Velasco F, Velasco AL, et al. Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. *Epilepsia* 2000;41:158-69.
3. Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 1997;48:1398-403.
4. Boroojerdi B, Prager A, Muellbacher W, Cohen LG. Reduction of human visual cortex excitability using 1 Hz transcranial magnetic stimulation. *Neurology* 2000;54:1529-31.
5. Lesser RP, Kim SH, Beyderman L, et al. Brief bursts of pulse stimulation terminate after-discharges caused by cortical stimulation. *Neurology* 1999;53:2073-81.
6. Ebert U, Ziemann U. Altered seizure susceptibility after high-frequency transcranial magnetic stimulation in rats. *Neurosci Lett* 1999;273:155-8.
7. Fleischmann A, Hirschmann S, Dolberg OT, Dannon PN, Grunhaus L. Chronic treatment with repetitive transcranial magnetic stimulation inhibits seizure induction by electro convulsive shock in rats. *Biol Psychiatry* 1999;45;759-63.
8. Akamatsu N, Fueta Y, Endo Y, Matsunaga K, Uozumi T, Tsuji S. Decre-

ased susceptibility to pentylenetetrazole-induced seizures after low frequency transcranial magnetic stimulation in rats. *Neurosci Lett* 2001;310:153-6.
9. Merton PA, Morton HB. Stimulation of the cerebral cortex in the intact human subject. *Nature* 1980;285:227.
10. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1985;1:1106-7.
11. Roth BJ, Saypol JM, Hallett M, Cohen LG. A theoretical calculation of the electric field induced in the cortex during magnetic stimulation. *Electroenceph Clin Neurophysiol* 1991;81:47-56.
12. Hallett M. Transcranial magnetic stimulation: a useful tool for clinical neurophysiology. *Ann Neurol* 1996;40:344-5.
13. Hallett M. Transcranial magnetic stimulation and the human brain. *Nature* 2000;406:147-50.
14. Rossini PM, Rossi S. Clinical applications of motor evoked potentials. *Electroenceph Clin Neurophysiol* 1998;106:180-94.
15. Chen R. Studies of human motor physiology with transcranial magnetic stimulation. *Muscle Nerve* 2000;Suppl 9:S26-S32.
16. Engel J. Inhibitory mechanisms of epileptic seizure generation. In: Fahn S, Hallett M, Lüders HO, Marsden CD. ed. *Advances in neurology Advances in Neurology 67.* Philadelphia PA: Lippincott-Raven 1995;157-171.
17. Kwan P, Sills GJ, Brodie MJ. The mechanisms of action of commonly used antiepileptic drugs. *Pharmacol Ther* 2001;90:21-34.
18. Joo EY, Kim SH, Seo DW, Hong SB. Zonisamide decreases cortical excitability in patients with idiopathic generalized epilepsy. *Clin Neurophysiol* 2008;119:1385-92.
19. Joo EY, Kim HJ, Lim YH, Ji KH, Hong SB, Zonisamide changes unilateral cortical excitability in focal epilepsy patients. *J Clin Neurol* 2010; 6:189-95
20. Pascual-Leone A, Hallett M. Induction of errors in a delayed response task by repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex. *Neuro Report* 1994;5:2517-20.
21. Chen R, Samii A, Canos M, Wassermann EM, Hallett M. Effects of phenytoin on cortical excitability in humans. *Neurology* 1997;49: 881-83.
22. Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. *Clin Neurophysiol* 2001; 112:1367-77.
23. Wassermann EM, Wedegaertner FR, Ziemann U, George MS, Chen R. Crossed reduction of human motor cortex excitability by 1-Hz transcranial magnetic stimulation. *Neurosci Lett* 1998;250:141-4.
24. Wu T, Sommer M, Tergau F, Paulus W. Lasting influence of repetitive transcranial magnetic stimulation on intracortical excitability in human subjects. *Neurosci Lett* 2000;287:37-40.
25. Berardelli A, Inghilleri M, Rothwell JC, Romeo S, Curra A, Gilio F, Modugno N, Manfredi M. Facilitation of muscle evoked responses after repetitive cortical stimulation in man. *Exp Brain Res* 1998;122: 79-84.
26. Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. *Exp Brain Res* 2000; 133:425-30.
27. Peinemann A, Lehner C, Mentschel C, Munchau A, Conrad B, Siebner HR. Subthreshold 5-Hz repetitive transcranial magnetic stimulation of the human primary motor cortex reduces intracortical paired-pulse inhibition. *Neurosci Lett* 2000;296:21-4.
28. Modugno N, Nakamura Y, MacKinnon CD, Filipovic SR, Bestmann S, Berardelli A, Rothwell JC. Motor cortex excitability following short trains of repetitive magnetic stimuli. *Exp Brain Res* 2001;140:453-9.
29. Pascual-Leone A, Houser CM, Reese K, Shotland LI, Grafman J, Sato S, Valls-Solè J, Brasil-Neto JP, Wassermann EM, Cohen LG, Hallett M. Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. *Electroenceph clin Neurophysiol* 1993;89:120-30.
30. Tergau F, Wanschura V, Canelo M, Wischer S, Wassermann EM, Ziemann U, Paulus W. Complete suppression of voluntary motor drive during the silent period after transcranial magnetic stimulation. *Exp Brain Res* 1999;124:447-54.
31. Menkes DL, Gruenthal M. Slow-frequency repetitive transcranial magnetic stimulation in a patient with focal cortical dysplasia. *Epilepsia* 2000;41:240-2.
32. Theodore WH, Hunter K, Chen R, et al. Transcranial magnetic stimulation for the treatment of seizures. A controlled study. *Neurology* 2000;59:560-2.
33. Wedegaertner F, Garvey M, Cohen LG, Hallett M, Wassermann EM. Low frequency repetitive transcranial magnetic stimulation can reduce action myoclonus. *Neurology* 1997;48:A119.
34. Joo EY, Han SJ, Chung SH, Cho JW, Seo DW, Hong SB. Antiepileptic effects of low-frequency repetitive transcranial magnetic stimulation by different stimulation durations and locations. *Clin Neurophysiol* 2007;118:702-8.