

ARE THE EFFECTS OF STIMULATION CATCHING?

Antikindling Effect of Slow Repetitive Transcranial Magnetic Stimulation in Rats

Anschel DJ, Pascual-Leone A, Holmes GL

Neurosci Lett 2003;351:9–12

The cerebrospinal fluid (CSF) of animals exposed to electroconvulsive shock (ECS) has anticonvulsant properties when injected into naive animals. The present study investigated whether the CSF of humans exposed to 1- or 10-Hz repetitive transcranial magnetic stimulation (rTMS) has similar properties. By using a 4-day rat flurothyl-kindling seizure model, we found that the kindling rate was significantly decreased by intraventricular injection of CSF from depressed patients exposed to 1-Hz rTMS. The CSF from patients that underwent 10-Hz rTMS showed a trend toward an increased kindling rate. These results support the similarity of ECS and rTMS and suggest that 1-Hz and 10-Hz rTMS produce distinct physiologic changes.

COMMENTARY

Recently considerable interest has been expressed in the use of direct brain stimulation to treat seizures—an interest probably encouraged by the clinical use of an indirect method, vagal nerve stimulation, and by the search for more effective methods of controlling epilepsy. Although some encouraging results have been observed (1), it is not clear how and why brain stimulation helps control seizures, especially because some brain stimulation can cause seizures (e.g., electroconvulsive therapy).

Anschel et al. therefore provide intriguing data. They found that kindling was delayed in Sprague–Dawley rats injected with cerebrospinal fluid (CSF) obtained from patients who had received brain stimulation, by using repetitive transcranial magnetic stimulation (rTMS). They reported that the main delay occurred on day 1 of kindling, not later. Finally, they reported that the delay was frequency specific: 1 Hz “worked,” 10 Hz did not. Stimulation was given as part of a study of the efficacy of rTMS in patients with medication-refractory depression.

The efficacy of rTMS for treating disease is uncertain (2,3). Putting this aside, the results are still interesting. First, the study suggests that stimulation has biochemical as well as physical effects on the brain. The authors speculate that an endogenous benzodiazepine-like substance, an opioid, or a small polypeptide might be involved. If the release of specific compounds can be shown and confirmed, is this release an effect limited to magnetic stimulation, or would the same thing occur with electrical stimulation? If differences exist between the substances released by electrical and magnetic stimulation, what are the differences?

Second, the effect on kindling was transient. Anschel et al. point out that this finding is consistent with the transient anticonvulsant effect of rTMS in humans (3). Is the antikindling effect transient because the released substance is metabolized quickly—both in humans and in rats? Could another substance that lasted longer in the brain be an effective anticonvulsant?

Third, the antikindling effect was frequency specific. Are certain frequencies truly anticonvulsant, and others, not? Some data indicate that this is the case. In addition, considerable research has been performed on the changes in cortical excitability after rTMS (4). The meaning of these changes is not yet entirely clear, but an understanding of the mechanism may prove directly relevant to understanding how stimulation affects epilepsy.

As the authors state, the study is preliminary. Perhaps the effects of patient CSF on kindling were patient specific and not frequency specific. One could study this issue by using CSF from additional patients—for example, if enough patients could be found, a group stimulated at 1 Hz, a group stimulated at 10 Hz, and a group not stimulated. Such a study could help to clarify the relation between epilepsy and depression, as well as help to develop new methods to treat both conditions.

by Ronald P. Lesser, M.D.

References

1. Durand DM, Bikson M. Suppression and control of epileptiform activity by electrical stimulation: A review. *Proc IEEE* 2002;89:1065–1082.
2. Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: A review. *Clin Neurophysiol* 2001;112:1367–1377.

3. Theodore WH, Hunter K, Chen R, Vega-Bermudez F, Boroojerdi B, Reeves-Tyer P, Werhahn K, Kelley KR, Cohen L. Transcranial magnetic stimulation for the treatment of seizures: A controlled study. *Neurology* 2002;59:560–562.
4. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol* 1998;15:333–343.