The failure of small-molecule antiepileptic drugs (AEDs) to effectively treat the symptoms of epilepsy in about one-third of patients with epilepsy has spawned the development of alternative treatment modalities. Among them, invasive surgical strategies are now routinely used in clinical practice. These include surgical resection of an epileptogenic focus (1) and electrical stimulation of either the vagus nerve or of deep brain structures using implanted electrodes (2). Although such invasive approaches have demonstrated benefits in a subset of patients; based on their nature, invasive strategies are necessarily associated with irreversible manipulations and bear inherent risks. For example, intracranial electrode implantation is associated with significant risks for brain hemorrhage and infection (5% risk, each) (3). Promising alternative strategies might in the future make use of unconventional noninvasive procedures, which remain understudied to date.

Repetitive transcranial magnetic stimulation (rTMS), direct current stimulation (tDCS) (4), and focal cooling (5) have received the most attention so far in preclinical and in a limited number of clinical studies. rTMS can be delivered via a handheld magnet and seems to be more effective in neocortical compared with mesial temporal foci, suggesting that penetration of the stimulus into deeper brain areas might be a limiting factor. tDCS is based on application of low current to the scalp via electrodes and, as in studies performed with rTMS, mixed results have been obtained (4). Focal cooling can be achieved by applying thermoelectric devices to the surface of the skull. This strategy is conceptually based on findings that hyperthermia (e.g., fever) promotes seizures, whereas hypothermia is known to protect the brain. Experimental data in animals are promising, but translation into a clinical setting remains a challenge (5).

In a new method paper, Min et al. describe a novel noninvasive strategy to reduce seizure activity by focused ultrasound sonication (FUS). The authors of this study used an air-backed, spherical ultrasound transducer operating at a frequency of 690 kHz to administer a low-intensity FUS (~130 mW/cm²) to a specified focal brain area. The acoustic intensity used in the experiment was sufficiently within the range of safety guidelines for the clinical ultrasound imaging. The occurrence of epileptic EEG bursts from epilepsy-induced rats significantly decreased after sonication when it was compared to the pre-sonication epileptic state. The PTZ-induced control group that did not receive any sonication showed a sustained number of epileptic EEG signal bursts. The animals that underwent sonication also showed less severe epileptic behavior, as assessed by the Racine score. Histological analysis confirmed that the sonication did not cause any damage to the brain tissue. CONCLUSIONS: These results revealed that low-intensity, pulsed FUS sonication suppressed the number of epileptic signal bursts using acute epilepsy model in animal. Due to its non-invasiveness and spatial selectivity, FUS may offer new perspectives for a possible non-invasive treatment of epilepsy.
triggered in adult rats using systemic application of 45 mg/kg pentylentetrazole (PTZ). Seizure activity was assessed via subdermal EEG electrodes and via Racine scoring. EEG activity was scored in 10-minute bins before PTZ application (baseline), after onset of PTZ-induced seizures, as well as during and after two 3-minute FUS applications, which were spaced by 10 minutes and targeted to the thalamus. Control animals were treated identically but did not receive FUS. Between-group and within-group treatment effects were determined.

In both comparisons, FUS sonication robustly reduced the average number of raw EEG peaks by 25-33% compared with values from pre-FUS seizures or from non-FUS control animals. Effects were stronger after the second FUS pulse and were more profound in the theta band. Suppression of epileptiform activity in the EEG was confirmed by a more than three-fold reduction of the Racine score a day after PTZ injection in the sonicated versus the nonsonicated groups. Sonication was not associated with any obvious signs of cell injury as validated by histology and DNA fragmentation analysis. These are important feasibility data suggesting that focused ultrasound, which is already used in a variety of different clinical applications (6), might have therapeutic potential for seizure suppression in epilepsy.

Although promising, the initial study by Min et al. has limitations, some of which warrant discussion here.

Epilepsy model. Focal ultrasound application to the thalamus was shown to be effective in suppressing epileptiform EEG activity in a model of acute PTZ-induced (generalized) seizures. Future work is needed to address the question of whether FUS would likewise be effective in suppressing spontaneous recurrent limbic (partial) seizures, preferably in a model of temporal lobe epilepsy. It might also be important to evaluate whether FUS might be effective in suppressing seizures that are resistant to conventional AEDs.

Duration of efficacy. EEG analysis was unfortunately limited to only 10-minute intervals following each of the FUS treatments. It would have been interesting to see how long the effects would last as well as to thoroughly study whether a second pulse provides additional benefit or merely adds up to a longer-lasting effect from the first stimulus.

Underlying mechanisms. Mechanisms that link ultrasound treatment with suppression of EEG activity were not studied in the investigation by Min et al. Potential mechanisms that have been discussed include mechanical disruption of synaptic contacts by ultrasound waves, regulation of thalamic GABAergic inhibitory neurons implicated in epileptogenic networks, or activation of voltage-gated or mechano-sensitive ion channels, which may lead to alterations in the membrane potential as a consequence of the ultrasound stimulation.

Alternatively, triggering the release of the brain's endogenous anticonvulsant adenosine might be considered as a putative mechanism responsible for the antiepileptic effect of focused ultrasound treatment. It has been shown in a variety of paradigms that any form of mechanical, physiological, or metabolic stress can augment adenosine signaling. The acute stress-induced adenosine response is physiologically important as an innate mechanism designed to protect the brain. In support of the hypothesis that augmentation of adenosine signaling might mechanistically be involved in the findings of Min et al., deep brain stimulation was shown to attenuate tremor by augmentation of adenosine signaling (7), acupuncture was shown to mediate local anti-nociceptive effects by augmentation of adenosine signaling (8), and metabolic stress induced by a ketogenic diet was shown to suppress seizures by augmentation of adenosine signaling (9). Therefore, it is tempting to speculate that ultrasound-induced mechanical stress to a tissue might likewise trigger a protective adenosine response.

Eventually, focused ultrasound treatment of epilepsy might constitute a promising avenue for further exploration. Apart from elucidating the underlying therapeutic mechanisms, it will be important to demonstrate versatility of the approach in different models of epilepsy, including models of pharmaco-resistant limbic epilepsy. Key advantages of this technology, such as safety, noninvasiveness, focused application, and accessibility of deeper brain structures, will theoretically permit the treatment of different types of focal epilepsies, and the treatment—being versatile—might be tailored to a patient's needs and combine cost-effectiveness with easy use.

by Detlev Boison, PhD

References

American Epilepsy Society

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Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
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This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

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2. First Name: Detlev  Last Name: Boison  Degree: PhD

3. Are you the Main Assigned Author? ☒ Yes  ☐ No

If no, enter your name as co-author:

4. Manuscript/Article Title: The Sound of Non-Invasive Seizure Control

5. Journal Issue you are submitting for: 11.6

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Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

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