To Stop the Seizure, You Must Become the Seizure: Closed-Loop Stimulation Phase Locked to Seizure Waves Disrupts Kindled Seizures While Open-Loop Stimulation Fails

Closed-Loop Stimulation of the Medial Septum Terminates Epileptic Seizures

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Temporal lobe epilepsy with distributed hippocampal seizure foci is often intractable and its secondary generalization might lead to sudden death. Early termination through spatially extensive hippocampal intervention is not feasible directly, because of the large size and irregular shape of the hippocampus. In contrast, the medial septum is a promising target to govern hippocampal oscillations through its divergent connections to both hippocampi. Combining this “proxy intervention” concept and precisely timed stimulation, we report here that closed-loop medial septum electrical stimulation can quickly terminate inrachipocampal seizures and suppress secondary generalization in a rat kindling model. Precise stimulus timing governed by internal seizure rhythms was essential. Cell type-specific stimulation revealed that the precisely timed activation of medial septum GABAergic neurons underlay the effects. Our concept of time-targeted proxy stimulation for intervening pathological oscillations can be extrapolated to other neurological and psychiatric disorders, and has potential for clinical translation.

Commentary

With almost a third of epilepsy patients refractory to antiepileptic drugs, there is a great need to find new means of stopping seizures. Responsive neurostimulation, where electrodes are placed in the brain and a small current is delivered whenever a seizure is detected, has been highly successful at stopping seizures in patients with intractable focal epilepsy. However, this approach is limited by the need to detect the seizure before it spreads throughout the brain, which can be difficult if the focal onset of each seizure is variable or if the electrodes are not placed in the seizure onset zone. Ideally, neurostimulation targets would project widely across the brain and terminate seizures even if they have already begun to spread. For this reason, Takeuchi and colleagues look to the medial septum as an ideal candidate for responsive neurostimulation in temporal lobe epilepsy. The medial septum is a midline structure that projects bilaterally and can control the activity of neurons widely across both temporal lobes. In this article, Takeuchi and colleagues demonstrate that medial septum electrical stimulation can terminate seizures in a rodent hippocampal kindling model of refractory temporal lobe epilepsy, but only under certain circumstances.

Takeuchi and colleagues found that the exact timing of medial septum electrical stimulation was absolutely critical for successfully terminating the seizures. To stop seizures, the stimulation had to be performed in a seizure-driven closed loop, where the stimulation was triggered by each spike, or wave, of the seizure. Interestingly, simply stimulating the medial septum during the seizure in an open-loop fashion at similar frequencies was not sufficient and, in some cases, even made the seizures worse. In other words, stimulation of the medial septum in the same range of frequencies had completely opposite effects on seizures depending on how (or rather, when) that stimulation was delivered. The authors next took a cell-type specific optogenetic approach to test whether GABAergic, glutamatergic, or cholinergic medial septum neurons were mediating this effect. They were able to successfully terminate seizures by optogenetically activating inhibitory, but not glutamatergic or cholinergic, medial septum neurons with their closed-loop system. Thus, the activation of inhibitory neurons is largely what underlies the seizure suppression effect from electrical stimulation of the medial septum. Together, these findings suggested that the timing of inhibition relative to the seizure waves was absolutely key to successfully controlling...
hippocampal and cortical seizures with medial septum intervention.

It is possible that the electrical stimulation could be stopping seizures by balancing bursts of excitatory drive with time-locked inhibition elicited by the medial septum stimulation. To test this hypothesis, the authors explored if introducing delays between seizure wave detection and stimulation delivery might change the efficacy of the closed-loop stimulation. Quite surprisingly, they found that varying the delay between 0 and 60 ms had no effect on how successful the closed-loop stimulation was at stopping seizures, suggesting that the closed-loop medial septum stimulation is not simply balancing the timing of excitation and inhibition, but may be disrupting the rhythmic networks that are driving the seizures. It is possible that the irregular pattern of the seizure waves, and thus the stimulation, could be what breaks the seizure network rather than its responsiveness. Indeed, it is possible that arrhythmic stimulation could turn the medial septum and its many downstream targets into desynchronizing hubs that balance pathological interregional synchronicity.

The role of synchrony in seizures is a topic of much debate as it is not clear whether the synchronization changes that occur in epilepsy are compensatory mechanisms or directly contribute to the initiation and spread of seizures. Notably, Takeuchi and colleagues found that the brain state during the time leading up to seizure induction predicted the success of the medial septum stimulation. Specifically, they found that closed-loop medial septum stimulation was less effective at stopping evoked seizures when the cortex or hippocampus had higher delta or theta power during the 30 seconds leading up to seizure induction. Thus, a more synchronous network may be primed to seize, and perhaps the desynchronized networks that have been observed in chronically epileptic rodents may be adaptive to reduce seizure thresholds. Indeed, successful reduction of seizures is associated with reduced theta power in the temporal lobe of patients after deep brain stimulation of the anterior nucleus of the thalamus. Given this relationship between the success of seizure termination and network synchronicity, it will be important to test whether closed-loop medial septum electrical stimulation can also effectively terminate spontaneously emerging seizures. This will be especially important since a recent paper showed that on-demand open-loop optogenetic activation of medial septal inhibitory neurons at 10 Hz was able to reduce the duration of spontaneous hippocampal seizures in the intrahippocampal kainate mouse model of temporal lobe epilepsy. Therefore, spontaneously emerging seizures may be more responsive to open-loop rhythmic stimulation than evoked seizures, though it remains untested whether closed-loop stimulation time-locked to seizure rhythms can also increase the efficacy of terminating spontaneously emerging seizures.

While responsive neurostimulation has been successful for people whose seizure foci are highly localized, finding options for those with multiple or traveling seizure foci remains a challenge. The findings of Takeuchi and colleagues indicate that responsive neurostimulation of the medial septum may be an effective and appropriate target, though perhaps only following certain stimulation protocols. Current applications of responsive neurostimulation detect seizure activity and immediately deliver a small current to the seizure focus. This work suggests that responsive neurostimulation therapies may be improved by instead delivering prolonged seizure-driven stimulation. Overall, this article establishes the medial septum as a strong candidate for efficient seizure termination with electrical stimulation and inspires further exploration of interventions that consider the timing of stimulation relative to seizures and other ongoing rhythms of the brain.

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