# Irritable No More: Activating Mossy Cells for the Treatment of Epilepsy

**Dentate Gyrus Mossy Cells Control Spontaneous Convulsive Seizures and Spatial Memory.**

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Temporal lobe epilepsy (TLE) is characterized by debilitating, recurring seizures and an increased risk for cognitive deficits. Mossy cells (MCs) are key neurons in the hippocampal excitatory circuit, and the partial loss of MCs is a major hallmark of TLE. We investigated how MCs contribute to spontaneous ictal activity and to spatial contextual memory in a mouse model of TLE with hippocampal sclerosis, using a combination of optogenetic, electrophysiological, and behavioral approaches. In chronically epileptic mice, real-time optogenetic modulation of MCs during spontaneous hippocampal seizures controlled the progression of activity from an electrographic to convulsive seizure. Decreased MC activity is sufficient to impede encoding of spatial context, recapitulating observed cognitive deficits in chronically epileptic mice.

**Commentary**

Over the past 30 years, we have learned quite a lot about the cellular features of mossy cells. Mossy cells are one of the most numerous and distinct cell types in the hippocampus, and one of two populations of glutamatergic neurons in dentate gyrus; the other population consists of the dentate granule cells (1). In acquired forms of epilepsy, a distinguishing feature of mossy cells is their selective vulnerability to traumatic injuries and epilepsy, a finding that has been observed in multiple species, including human (2, 3). Although they are found exclusively within the polymorph layer (hilus), mossy cells have extensive local and long-range projections to the ipsilateral and contralateral dentate gyrus, where they innervate both glutamatergic granule cells and inhibitory interneurons (4–7). As such, they are positioned to either excite or inhibit large populations of granule cells, depending on whether their direct excitatory contacts onto granule cells or their projections to local inhibitory neurons dominate. This complex circuitry has made it difficult to predict their network functions in vivo, especially in the context of acquired epilepsies where cell loss and synaptic reorganization are major features (8). Another problem is that it has been technically challenging to selectively target mossy cells for manipulations using available methods.

Bui and colleagues used a series of carefully designed optogenetics-based experiments to dissect the role of mossy cells in hippocampal seizures and memory. Their strategy was similar to the authors' prior ground-breaking work showing spontaneous seizures could be stopped in real time by activating inhibitory neurons or inactivating principal neurons in hippocampus of chronically epileptic mice (9, 10). In this study, Bui and colleagues used two creative approaches to selectively manipulate mossy cell activity in normal mice and in the intrahippocampal kainic acid model of acquired epilepsy. First, they took advantage of the unique anatomy of mossy cells, using wheat germ agglutinin (WGA)–Cre system to express the inhibitory archaerhodopsin (ArchT) only in commisurally projecting mossy cells. In other experiments, a virus containing the excitatory channelrhodopsin (ChR2) was delivered directly into the hilus of calcitonin receptor-like (Crlr) Cre mice. While the authors confirmed that both approaches selectively targeted mossy cells in the dentate gyrus, it is important to note that WGA is capable of being transported bidirectionally (11) and a small portion of CA3 neurons may also show Cre expression in the Crlr mouse line (12). Activating mossy cells in dorsal, but not ventral, hippocampus reduced the duration of spontaneous electrographic nonconvulsive seizures, whereas silencing mossy cells had no effect. However, this effect was not as strong as inhibiting granule cells directly. While inactivating mossy cells at the onset of electrographic seizures promoted generalization to convulsive behavioral seizures, mossy cell activation reduced their occurrence. Interestingly, convulsive seizures also could be induced by optogenetically driving granule cell activity, but granule cell inhibition had no effect on seizure generalization. Finally, mossy cell inactivation in normal mice produced deficits in memory encoding (but not retrieval) of a novel object spatial memory task. These behavioral deficits were comparable to those observed in epileptic animals.

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Whether optogenetic manipulations could restore cognitive performance in epileptic mice was not tested. Altogether, these data support the general hypothesis that driving mossy cell activity has an overall inhibitory effect on granule cells and that mossy cells are active participants in seizure generalization and spatial memory encoding.

The contributions of mossy cells to behavior has been the subject of much debate, and a number of interesting circuit-level questions emerge from these studies. The dentate gyrus plays an important role in filtering information entering into the hippocampus from the entorhinal cortex. Perhaps driving mossy cell activity would enhance this filtering capability by exerting an overall inhibitory influence on granule cells. It would be interesting to explore how network activity or rhythmogenesis in the hippocampus is shaped by mossy cell manipulations in real time during hippocampus-dependent learning and memory behaviors. For example, in anesthetized rats, mossy cell activity is phase-locked to theta oscillations in vivo (13), and in epileptic rats mossy cells are capable of generating abnormal epileptiform burst discharges synchronized with CA3 pyramids (14). In light of the new data from Bui and colleagues, it is timely to ask whether delivering different patterns of stimulation to mossy cells could produce an excitatory versus inhibitory influence over granule cells. Given their extensive projections and the relatively focal light delivery, it is also intriguing to ask what would happen if a larger cohort of mossy cells were activated (or inactivated). Perhaps a more robust effect on seizure dynamics could be achieved by activating a greater number of mossy cells. Nevertheless, this new study by Bui and colleagues supports the loss of mossy cells as a contributing factor to seizures in temporal lobe epilepsy.

Advances in nonpharmacologic approaches to treat epilepsy are rapidly advancing toward the clinic. A large variety of brain cell types have now been successfully targeted for preclincal optogenetics-based epilepsy therapy. As this emerging technology is further refined, the field will need to address an important question of how we decide which cell types, brain regions, behavioral co-morbidities, or even the forms of epilepsy to target for therapy in humans. Nevertheless, this basic science study provides a number of exciting new insights into the function of mossy cells in vivo.

*by Young J. Kim and Robert F. Hunt*

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