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Controlling learning and epilepsy together:

Silencing dentate gyrus mossy cells affects spatial learning as well as seizures

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The dentate gyrus (DG) is a region in the hippocampus of the brain that is important for many cognitive functions, such as spatial learning and memory, and understanding our environment or context (1). The DG is also considered to be important in many diseases, some of which surprisingly do not appear to be related to memory, such as temporal lobe epilepsy (TLE) (2). One explanation is based on the idea that the DG is an inhibitory filter or gate (3, 4), preventing too much information from corrupting memory formation as well as preventing seizures. However, it is unclear exactly how and when the DG limits the influence of afferent input to the hippocampus, and when the DG is permissive, because the DG has powerful excitatory and inhibitory characteristics. For example, the DG contains mossy cells (MCs), which have both characteristics (5). On page XXX of this issue, Bui *et al.* (6) show that silencing MCs impairs a spatial memory task and also terminates seizures in an animal model of TLE, which could improve our understanding of TLE as well as cognitive comorbidities.

MCs project primarily to excitatory granule cells (GCs), which are the principal cell type and major output of the DG (see the figure). GCs project to the CA3 area of the hippocampus, which in turn activates other areas of the hippocampus and extrahippocampal regions to carry out functions related to memory and also to cause seizure spread throughout the brain. Because MCs produce the excitatory neurotransmitter glutamate, they can activate GCs. However, MCs also activate neurons that produce the inhibitory neurotransmitter γ -aminobutyric acid (GABA) and these GABAergic neurons, such as basket cells, can inhibit GCs (5).

Many of the hypotheses for the functions of MCs have come from studies in animal models of TLE-like conditions in which MCs are reduced in number, so the normal function of MCs can potentially be inferred. The dormant basket cell hypothesis proposes that without MCs, basket cells lack sufficient input to maintain GC inhibition (7). By contrast, the irritable MC hypothesis suggests that when MC numbers are reduced by brain injury, the surviving MCs become “hyperexcitable” and cause hyperactivity of GCs (8).

After these hypotheses were proposed, MC manipulations brought new insights (9), but the roles of MCs in normal DG function and TLE remained unclear. Bui *et al.* used several approaches to investigate. They induced a TLE-like condition in mice by injecting the

glutamate receptor agonist and excitotoxin kainic acid into the dorsal DG to create a seizure focus. Kainic acid induces many changes to the DG, including damage to MCs, and ultimately these changes transform the brain into one that has spontaneous intermittent seizures (chronic epilepsy). Some of these seizures can be severe, causing convulsions. By pulsing light over the DG using implantable optic fibers, Bui *et al.* determined if exciting or inhibiting residual MCs, engineered to respond to light, would alter seizures. They also used closed-loop optogenetics, an ingenious method in which an algorithm identifies the onset of a seizure and triggers pulses of light to try and stop the seizure. MC excitation reduced the duration of electrographic seizures, which are unaccompanied by convulsions. Activating MCs also reduced the propensity for a seizure to become convulsive. This suggests that MCs primarily inhibit GCs, preventing persistent activation of downstream areas in the hippocampus, consistent with the dormant basket cell hypothesis.

In an effort to understand how MCs control seizures and convulsions, the authors activated or silenced the GCs. Surprisingly, silencing GCs did not stop the emergence of convulsive seizures. The likely explanation of this apparent paradox lies—as the authors suggest—in anatomical connections. A single MC projects to GCs that are in both the ipsilateral and contralateral DG, but a single GC only projects locally within the hippocampus. This explanation is incomplete, however, because GCs in one small region project to both MCs and CA3 pyramidal cells that have wide-ranging projections. Even some GABAergic neurons project for long distances and they are often lost or altered after epilepsy (10, 11), possibly disinhibiting neurons outside the DG that are part of a circuit that underlies a seizure. These complexities may be explained after additional aspects of the circuitry and physiology in the TLE model become clear.

An important clinical concern in patients with TLE is cognitive comorbidities, which accompany chronic seizures. Bui *et al.* investigated this by optogenetically silencing MCs in normal mice to see if impairments could be induced in tasks that test cognitive ability. Silencing MCs caused deficits in a task that tests spatial memory, where a mouse must detect changes in the location of an object. Interestingly, they had to silence MCs during the learning phase of the task to see an effect, suggesting that learning (or encoding) of an object's location, but not the memory of it, is dependent on MCs. How MCs affect learning could be related to their unique sensitivity to cortical afferent input (5). It will be interesting to determine if deficits in the TLE mice can be alleviated by activating MCs during learning.

Thus, Bui *et al.* provide some answers but also leave us with some questions. For example, how do MCs control only the duration of electrographic seizures? The reason may be similar to the reason MCs control convulsive seizures—in each case they terminate the seizure prematurely. It could be that activating surviving MCs might strengthen the DG inhibitory gate sufficiently to stop a seizure that has begun. However, how could a very small number of MCs stop a seizure that involves so many neurons in different brain regions? A possible explanation is that MCs that survive in the mouse model of TLE begin to grow additional connections (sprouting), which is known to happen in other cell types, such as GCs (2). Indeed, what would occur if all MCs survived in this model? Would MCs still inhibit GCs, or would they activate them? And would seizures be affected?

Other aspects of the DG that affect object location memory and convulsive seizures are also intriguing. For example, the DG is one of the few areas of the brain where GC neurogenesis occurs throughout life. Remarkably, new GCs influence the ability to distinguish novelty (12), which seems related to the functions of MCs to encode new object locations, identified by Bui *et al.* Reduction of new GCs in an adult mouse also enhances the susceptibility to convulsive seizures induced by systemic kainic acid injection (13). MCs make the first excitatory synapses on new GCs (13), so MC interactions with new GCs could play a role in spatial encoding and seizure susceptibility. Interestingly, GCs release peptides and even GABA, as well as undergoing many other changes, after seizures in mice (14). This might help explain why MC and GC manipulations had some different consequences in TLE mice. Further investigation should advance our understanding of how the DG contributes to memory and its role in epilepsy.

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Linking seizures and memory

MCs excite GCs and GABAergic neurons, which MCs excite GCs and GABAergic neurons, which inhibit GCs. Thus, MCs can activate many GCs or inhibit GCs. Thus, MCs can activate many GCs or they can inhibit them, via GABAergic neurons such as they can inhibit them, via GABAergic neurons such as basket cells. This cellular circuitry can excite many basket cells. This cellular circuitry can excite many parts of the DG, potentially leading to activation of parts of the DG, potentially leading to activation of CA3 pyramidal cells in the hippocampus and their downstream targets, to initiate a seizure.