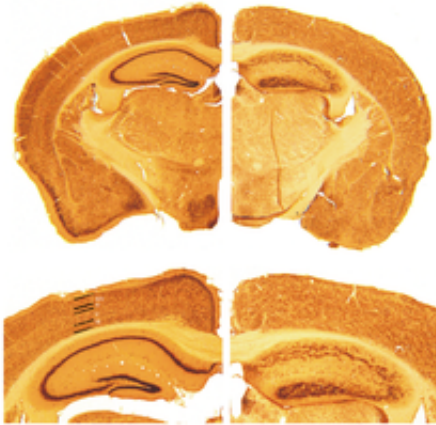


Epilepsy sends differentiated neurons on the run

29 March 2013, by John Hewitt



Credit: Wikipedia Commons

(Medical Xpress)—The smooth operation of the brain requires a certain robustness to fluctuations in its home within the body. At the same time, its extraordinary power derives from an activity structure poised at criticality. In other words, it is highly responsive to many low-threshold events. When forced beyond its comfort zone in parameter space—its operating temperature, electrolytes, sugars, blood gas or even sensory input—the direct result is seizure, coma, or both. It would appear that anything rendered too hot or cold, too concentrated or scarce, precipitates seizure. In those genetically predisposed, or compromised by head trauma, the seizing tends toward full-blown epilepsy. A group in Hamburg, led by Michael Frotscher has been chipping away at the causes of common form a epilepsy, temporal lobe epilepsy (TLE). Their latest research published in the journal, *Cerebral Cortex*, takes a closer at differentiated neurons in the dentate gryus of mouse hippocampus. Once thought to be completely immobilized by virtue of their broadly integrated dendritic trees, these neurons are now shown to become migratory once again in direct

response to seizure activity.

[Genetic predisposition](#) to seizure can come in the form of ongoing chemical or metabolic imbalance due to defects in enzymes, [ion channels](#) or receptors. Alternatively it manifests through direct structural defect as a result of a developmental flaw. In slice preparations, Frotscher looked at a particular form of TLE, where the granule cell layer (GCL) in the dentate gyrus is disrupted. The cells there have either failed to migrate along glial scaffolds into a compact layer with clearly defined margins, or aberrant clumps of cells congregate in the wrong places. Seizures secondary to fever have been known to cause this aberrant migration of granule cells, as has a particular kind of mouse mutant known as the reeler mouse.

The catalog of mouse mutants is expansive; it is a veritable library of hopeless monsters. [The reeler mutant](#), known since 1951, has a unique set of issues wherein cells fail to migrate to the right spots in the cerebellum, cortex, and [hippocampus](#). The protein, reelin was later discovered as one of the causes of [this particular phenotype](#). Reelin is an extracellular matrix protein which initially provides scaffolding for neuron migration, and later a fence to fix neurons in place. In mice with mutated reelin protein, cells in all parts of the hippocampus, not just the dentate gyrus are spread out into a broad and diffuse layer.

By injecting kainate (KA), an excitotoxin that predictably results in seizures, into the dentate gyrus, Frotscher biased the granule cells into entering a phase of bursting activity. With their glutamate receptors fully activated by KA, the granule cells fire rapid volleys of spikes followed by deep depolarization periods. Cells that had been fluorescently labeled with GFP and observed with real time video microscopy were also seen to become motile and dispersed. The normal band of granule cells doubled, or tripled, in thickness. Next, Frotscher looked for a link between this response to

KA and the reelin protein. Both reelin mRNA and reelin immunoreactivity were found to be reduced in the dentate granule cells that had been dispersed by KA.

Against this tableau of complex responses to KA, is the fact that adult neurogenesis of dentate granule cells occurs within many mammalian species. A narrowly-defined rostral migratory stream normally delivers fresh cells to both the dentate gyrus and olfactory bulb. Application of BrdU, a marker of newly born cells, labeled microglial and astrocytes near the site of injection, but only a few of the [granule cells](#). As an excitotoxin, KA may be expected to kill at least some cells outright, and cause significant dendritic degeneration in many more. An interesting question to ask, is how does KA induce granule cell dispersion despite the dense interconnections with their neighbors?

During KA induced motility, the nucleus was typically observed to translocate within the cell into one of the dendrites, pulling the soma along with it. This process is believed to involve a myosin-dependant forward flow of actin structural protein within the cell. Outside the cell, changes to the reelin matrix appear to be involved as well. One potential mechanism that has emerged is that reelin induces serine phosphorylation of cofilin, an actin-associated protein involved in depolymerization. The authors conclude reelin-induced cofilin phosphorylation controls neuronal migration during development, and prevents abnormal motility in the mature brain.

Undoubtedly many mechanisms are involved in the KA-induced seizure and reelin story. Other cell types in the [dentate gyrus](#) need to be looked at in closer detail. For example, how reelin expression is regulated, and which cells manufacture it are current areas of study. It is important as well to differentiate between the causes of seizure, and its consequences. On paper they can be neatly packaged concepts but in the real tissue, and in intact animals, they can be anything but.

More information: Epilepsy-Induced Motility of Differentiated Neurons, *Cereb. Cortex* (2013) [doi: 10.1093/cercor/bht067](https://doi.org/10.1093/cercor/bht067) First published online: March 15, 2013.

Abstract

Neuronal ectopia, such as granule cell dispersion (GCD) in temporal lobe epilepsy (TLE), has been assumed to result from a migration defect during development. Indeed, recent studies reported that aberrant migration of neonatal-generated dentate granule cells (GCs) increased the risk to develop epilepsy later in life. On the contrary, in the present study, we show that fully differentiated GCs become motile following the induction of epileptiform activity, resulting in GCD. Hippocampal slice cultures from transgenic mice expressing green fluorescent protein in differentiated, but not in newly generated GCs, were incubated with the glutamate receptor agonist kainate (KA), which induced GC burst activity and GCD. Using real-time microscopy, we observed that KA-exposed, differentiated GCs translocated their cell bodies and changed their dendritic organization. As found in human TLE, KA application was associated with decreased expression of the extracellular matrix protein Reelin, particularly in hilar interneurons. Together these findings suggest that KA-induced motility of differentiated GCs contributes to the development of GCD and establish slice cultures as a model to study neuronal changes induced by epileptiform activity.

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