

### HIPPOCAMPAL PLACE CELLS IN EPILEPTIC RATS SHOW ALTERATIONS IN ACTIVITY: A POSSIBLE CLUE TO DECREASED MEMORY PERFORMANCE

#### Seizure-induced Changes in Place Cell Physiology: Relationship to Spatial Memory

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Status epilepticus (SE) is a frequent neurologic emergency associated with a significant risk of morbidity in survivors. Impairment of hippocampal-specific memory is a common and serious deficit occurring in many of the survivors. However, the pathophysiologic basis of cognitive deficits after SE is not clear. To address the cellular concomitants of spatial memory impairment directly, we recorded the activity of place cells from CA1 in freely moving rats subjected to SE during early development and compared this activity with that in control rats. Place cells discharge rapidly only when the rat's head is in a cell-specific part of the environment called the "firing field." This firing field remains stable over time. Normal place cell function seems to be essential for stable spatial memory for the environment. We therefore compared place cell firing patterns with visuospatial memory in the water maze in SE and control rats. Compared with controls, place cells from the SE rats were less precise and less stable. Concordantly, the water-maze performance also was impaired. A close relation was noted between precision and stability of place cells and water-maze performance. In contrast, a single, acute, chemically induced seizure produced cessation of place cell activity and spatial memory impairment in water-maze performance that reversed within 24 hours. These results strongly bolster the idea that a relation exists between abnormal place cells and spatial memory. Our findings also suggest that the defects in place cell and spatial memory after SE and acute chemically induced seizures result from different processes.

#### COMMENTARY

Patients with the mesial temporal lobe or limbic epilepsy syndrome often have memory deficits of various forms. These decreases in memory function have been correlated with the degree of atrophy in the hippocampus on magnetic resonance imaging (MRI) scans or the severity of neuronal loss in surgical specimens. Memory loss also has been correlated with slowing on EEG or decreased event-related potentials. Whereas it has been assumed that the memory impairment is related to neuronal loss, this has not been proven, and the cause of memory dysfunction in epilepsy is still largely a mystery. It is with this background that the article by Liu et al. is a welcome contribution to the field of epilepsy research, as it begins to provide insight into the cellular mechanisms responsible for epilepsy-related memory dysfunction.

Numerous studies have demonstrated that lithium-pilocarpine-induced status epilepticus in rats is associated with neuropathologic changes, similar to those occurring in human limbic epilepsy, as well as with significant deficits in learning and memory. In the series of experiments by Liu et al., rats subjected to lithium-pilocarpine-induced status epilepticus as adolescents developed chronic limbic epilepsy, exhibiting recurrent seizures. Hippocampal place cell activity was compared with changes in learning and memory and the neuropathologic changes that occur in these animals.

The existence of hippocampal place cells has been well known in the psychology literature for many years. Place cells are neurons, identified by extracellular unit recordings, that fire action potentials when rats are in a particular part (and, at times, orientation) of a familiar environment. The increased activity of place cells, which occurs only when the rat is in the cell's "firing field," is maintained over repeated testing and over a number of days. The mechanisms accounting for the specific physiologic responsiveness of place cells are not well understood, but the place cell phenomenon is well established and robust. In the present study, the authors found that the relative proportion of place cells, among all recorded neurons, was the same between epileptic and control animals, but that in the epileptic animals, significantly less precision (i.e., the area over which the place cells responded was larger) and more inconsistency (i.e., with repeated testing, the region over which the place cells were active

was more variable) were noted in their behavior. In addition, this dysfunction correlated well with decreased learning and memory (as assessed in a water-maze test) and with the severity of hippocampal neuronal loss and mossy fiber sprouting.

How are we to interpret these correlations among altered physiology, decreased behavioral performance, and anatomic changes? What are the functional consequences of altered place cell behavior? The basis for place cell activity is still not well understood. However, it can be viewed as a measure of the function of a particular population of neurons in a complex network, involving spatial orientation, recognition of the orientation, and an encoding process—the latter aspect of which also may be involved in memory formation. The changes ob-

served in the epileptic animals demonstrate that the activity of the place cells in this network is less precise and less consistent than normal, which could in some way interfere with the encoding of memories. Do the findings have a direct interpretation in terms of memory dysfunction in epilepsy? Of course not, but they do suggest that a measurable physiologic dysfunction occurs in part of the circuitry that supports memory. Importantly, Liu et al. uncovered a new tool, which can be used in studies to define *where* the critical dysfunction lies within neural circuits involved in memory formation and storage as well as *how* the dysfunction occurs.

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