CURRENT LITERATURE

DORMANT BASKET CELL HYPOTHESIS REVISITED . . . AGAIN

"Dormant Basket Cell" Hypothesis Revisited: Relative Vulnerabilities of Dentate Gyrus Mossy Cells and Inhibitory Interneurons after Hippocampal Status Epilepticus in the Rat

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The "dormant basket cell" hypothesis suggests that postinjury hippocampal network hyperexcitability results from the loss of vulnerable neurons that normally excite insult-resistant inhibitory basket cells. We have reexamined the experimental basis of this hypothesis in light of reports that excitatory hilar mossy cells are not consistently vulnerable, and inhibitory basket cells are not consistently seizure resistant. Prolonged afferent stimulation that reliably evoked granule cell discharges always produced extensive hilar neuron degeneration and immediate granule cell disinhibition. Conversely, kainic acid–induced status epilepticus in permanently implanted animals produced similarly extensive hilar cell loss and immediate granule cell disinhibition, but only when granule cells discharged continuously during status epilepticus. In both preparations, electron microscopy revealed degeneration of presynaptic terminals forming asymmetric synapses in the mossy cell target zone, including some terminating on γ-aminobutyric acid–immunoreactive elements, but no evidence of axosomatic or axoaxonic degeneration in the adjacent granule cell layer. Although parvalbumin immunocytochemistry and in situ hybridization revealed decreased staining, this apparently was due to altered parvalbumin expression rather than to basket cell death, because substance P receptor–positive interneurons, some of which contained residual parvalbumin immunoreactivity, survived. These results confirm the inherent vulnerability of dendritically projecting hilar mossy cells and interneurons and the relative resistance of dentate inhibitory basket and chandelier cells that target granule cell somata. The variability of hippocampal cell loss after status epilepticus suggests that altered hippocampal structure and function cannot be assumed to cause the spontaneous seizures that develop in these animals and highlights the importance of confirming hippocampal pathology and pathophysiology in vivo in each case.

COMMENTARY

Since its initial formulation, the dormant basket cell hypothesis has inspired intense investigation and controversy. The hypothesis was formulated to explain loss of paired-pulse inhibition of hippocampal dentate granule cells and hyperexcitable responses in these neurons after prolonged perforant path stimulation. This treatment also resulted in the death of hilar mossy cells, which are excitatory, whereas inhibitory basket cells in the granule cell layer were preserved. One explanation for loss of paired-pulse inhibition and hyperexcitability of dentate granule cells after perforant path stimulation is that loss of mossy cells results in reduction of afferent excitatory drive onto basket cells, rendering them "dormant" and granule cells hyperexcitable.

Although the hypothesis was formulated to explain experimental findings in the perforant path stimulation model of epilepsy, it has come to be regarded as a grand unifying hypothesis in epilepsy research for various reasons. Neurologic injuries that result in hyperexcitable responses in hippocampal neurons often also result in loss of hilar mossy cells. Reduction of γ-aminobutyric acid (GABA)-mediated inhibition reliably results in seizures, and several currently used anticonvulsants enhance it. Finally, reduction of GABA-mediated inhibition was demonstrated in some chronic temporal lobe epilepsy models and during status epilepticus.

Intense testing of the hypothesis in different experimental models of epilepsy has also resulted in a lively debate in print and at scientific meetings. Three broad criticisms of the hypothesis have emerged: first, it is suggested that many mossy cells survive neurologic insults that result in hyperexcitability; second, in some models, a loss GABAergic interneurons was demonstrated; and finally, electrophysiologic recordings from granule cells in hippocampal slices from epileptic animals reveal normal or even enhanced inhibitory postsynaptic responses. In this study, Sloviter and colleagues very carefully reevaluate relative vulnerability of mossy cells and basket cells

in the perforant path stimulation model and confirm their earlier findings. Interestingly, when this analysis was extended to the kainic acid model of temporal lobe epilepsy, mossy cell loss was more variable and depended on the extent of dentate granule cell activation. The study does not test a key aspect of the hypothesis: does the perforant path stimulation render basket cells dormant? Electrophysiologic recordings from basket cells in stimulated animals could reveal whether the excitatory input to these neurons and their spontaneous firing rate is diminished.

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