SEIZURE-INDUCED NEUROGENESIS AND EPILEPSY: INVOLVEMENT OF ECTOPIC GRANULE CELLS?

Perforant-path Activation of Ectopic Granule Cells That Are Born after Pilocarpine-induced Seizures

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Granule cells in the dentate gyrus are born throughout life, and various stimuli can affect their development in the adult brain. After seizures, for instance, neurogenesis increases greatly, and some new cells migrate to abnormal (ectopic) locations, such as the hilus. Previous electrophysiological studies of this population have shown that they have intrinsic properties that are similar to those of normal granule cells, but differ in other characteristics, consistent with abnormal integration into host circuitry.

To characterize the response of ectopic hilar granule cells to perforant-path stimulation, intracellular recordings were made in hippocampal slices from rats that had pilocarpine-induced status epilepticus and subsequent spontaneous recurrent seizures. Comparisons were made with granule cells located in the granule cell layer of both pilocarpine- and saline-treated animals. In addition, a few ectopic hilar granule cells were sampled from saline-treated rats. Remarkably, hilar granule cells displayed robust responses, even when their dendrites were not present within the molecular layer, where perforant-path axons normally terminate.

The evoked responses of hilar granule cells were similar in several ways to those of normally positioned granule cells, but some differences were found. For example, an unusually long latency was seen to onset of responses evoked in many hilar granule cells, especially those without molecular layer dendrites. Presumably this is due to polysynaptic activation by the perforant path. These results indicate that synaptic reorganization after seizures can lead to robust activation of newly born hilar granule cells by the perforant path, even when their dendrites are not in the terminal field of the perforant path. Additionally, the fact that these cells can be found in normal tissue and develop similar synaptic responses suggests that seizures, although not necessary for their formation, strongly promote their generation and the development of associated circuits, potentially contributing to a lowered seizure threshold.

COMMENTARY

Over the last 5- to10-year period, the role that neurogenesis may play in the process of epileptogenesis has been extensively discussed. Morphologic observations by Parent and colleagues after pilocarpine-induced status epilepticus (1) and after kindling (2) initially suggested that the phenomenon of mossy fiber sprouting could be due to the growth of axons from newly born granule cells (i.e., neurogenesis) rather than to the formation of collateral axons from granule cells that were already present before the experimental status epilepticus. This hypothesis was based, in part, on evidence that the newly formed granule cells project to the inner molecular layer, as seen with the Timm stain and other markers. Subsequent studies by these researchers showed that robust Timm stain was still present in the inner molecular layer after irradiation that blocked neurogenesis (3); therefore, substantial mossy fiber growth in the inner molecular layer was from granule cells that were present before the experimental status epilepticus. Nonetheless, it remains possible that newly born granule cells participate in reorganized synaptic circuits that might contribute to epileptogenesis.

These initial concepts about the hypothetical role of neurogenesis in temporal lobe epilepsy were based on little or no functional data. This study by Scharfman and her collaborators, however, is part of a series of articles (4,5) suggesting that newly generated granule cells are actively involved in hippocampal integration and participate in the spontaneous seizures of pilocarpine-treated rats. This study, based on intracellular recordings from ectopic hilar granule cells, provides evidence that newly born granule cells (i.e., generated after pilocarpine-induced status epilepticus) receive excitatory synapses from the major input to the dentate gyrus, the perforant path.

Do the ectopic hilar granule cells become part of a new recurrent excitatory circuit? The presence of complex or multicomponent excitatory postsynaptic potentials in the ectopic

hilar granule cells from the pilocarpine-treated rats, but not from the control animals, suggests that these neurons receive *abnormal* excitatory synaptic inputs, as would be expected in a new recurrent excitatory circuit. Ectopic hilar granule cells that did not have a dendrite in the inner molecular layer appeared to receive input from other excitatory neurons (i.e., granule cells, mossy cells, and/or CA3 pyramidal cells) because their excitatory postsynaptic potentials had a long latency, as would be expected if the input was polysynaptic. Therefore, the ectopic hilar granule cells appear to receive synaptic input from a new recurrent excitatory circuit, involving nearby neurons that have formed during epileptogenesis.

Were the recorded neurons actually newly born granule cells? The recorded neurons had the electrical and morphologic properties of dentate granule cells but were located ectopically in the hilus. As Scharfman and colleagues point out, the normal and control rats also had ectopic granule cells, and many of their electrical properties were quite similar to those from the ectopic granule cells of the pilocarpine-treated rats. The main argument in support of the hypothesis that the ectopic hilar granule cells were newly born (i.e., after the experimental status epilepticus) is that more of them were present in the pilocarpine-treated rats than in the control animals. Thus some of the ectopic hilar granule cells in the pilocarpine-treated rats could have been part of the original population (i.e., were present before the pilocarpine treatment), but it would seem that the others had to have been born after the pilocarpine treatment or had to have migrated to the hilus as adult granule cells. Thus the weight of the evidence in these studies is consistent with the hypothesis that the ectopic hilar granule cells were newly formed and that they received abnormal excitatory synaptic inputs.

An important question, which was not within the scope of the work by Scharfman and co-workers, is whether these ectopic hilar granule cells *make* excitatory synaptic connections that could cause seizures to propagate through the dentate gyrus. For example, it would be interesting to know whether these newly formed granule cells project their axons to other granule cells or to interneurons with dendrites in the inner molecular layer, as was suggested in the original reports on this phenomenon (1,2). If so, this would imply that the newly formed ectopic granule cells become *fully integrated* into the hippocampal circuitry—both receiving *and projecting* excitatory synaptic connections.

Because the ectopic granule cells are located in the hilus (a site where neurons typically are lost in temporal lobe epilepsy), neurogenesis effectively may replace lost hilar neurons, but replace them with neurons that make abnormal connections. One central question is whether the newly formed ectopic hilar granule cells of pilocarpine-treated rats essentially become like the preexisting granule cells in stratum granulosum or whether they show abnormalities that are greater than those of the other granule cells in epileptic rats. If they are more abnormal than the other granule cells that were in place before the status epilepticus, then the mechanism of seizure-induced neurogenesis and the presence of these newly formed granule cells would seem to be an important contribution to the process of epileptogenesis. If, however, they are similar to the other granule cells that already appear to be involved in abnormal recurrent excitatory circuits, then it would imply that eliminating these neurons (i.e., blocking formation of the ectopic granule cells) might not alter the epileptogenic properties of the dentate gyrus. Thus, future studies (similar in nature to the present work by Scharfman and her collaborators) on the participation of newly formed granule cells in dentate circuitry could potentially address the issue of the hypothetical importance of seizure-induced neurogenesis in temporal lobe epilepsy.

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References

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