

ENVIRONMENTAL FACTORS INFLUENCE NEUROGENESIS AND MODIFY THE COGNITIVE OUTCOME AFTER STATUS EPILEPTICUS

Memory Impairment Following Status Epilepticus in Immature Rats: Time-Course and Environmental Effects

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Status epilepticus (SE) has a high mortality and morbidity rate in children. Disturbances in learning and memory are frequently associated with SE, although it is not clear when the cognitive deficits occur. If cognitive dysfunction occurs immediately after the seizure, the window of opportunity for therapeutic intervention is limited. The first goal of this study was to determine the timing of cognitive dysfunction after SE in weanling rats. As there is evidence that enriching the environment can improve cognitive and motor deficits after brain injury, our second goal was to determine whether environmental enrichment improves cognitive function after SE. Rats underwent lithium-pilocarpine-induced SE at postnatal (P) day 20 and were then tested for visual-spatial memory in the water maze at P22, P25, P30, or P50. Rats with SE performed significantly worse in the water maze than did control rats at all time points. Once the time courses of visual-spatial memory deficits were determined, a second group of P20 rats were subjected to SE and were then placed in an enriched environment (enriched group) or remained in standard cages in the vivarium (nonenriched group) for 28 days. After environmental manipulation, the animals were tested in the water maze. Rats housed in an enriched environment after the SE performed substantially better in the water maze than did rats housed in standard cages. However, no differences were found between the enriched and nonenriched groups in EEG or histologic evaluation. Although SE results in cognitive impairment within days of the seizure, housing in an enriched environment after SE has a beneficial effect on cognitive performance in rats.

Delayed Kindling Epileptogenesis and Increased Neurogenesis in Adult Rats Housed in an Enriched Environment

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Environmental risk factors such as stressful experiences have long been recognized to affect seizure susceptibility, but little attention has been paid to the potential effects of improving housing conditions. In this study, we investigated the influence of an enriched environment on epileptogenesis. Epileptic susceptibility was assessed in animals housed in an enriched environment either before or during (group I) or only during (group II) a kindling procedure and in animals placed in isolated conditions (group III). The kindling paradigm provides a reliable assessment of the capacity to develop seizures after repeated daily low-frequency electrical stimulations. As both enriched environment and seizures are known to interfere with hippocampal neurogenesis, the number of newly generated dentate cells was assessed before and after the kindling procedure to investigate in more detail the relation between epileptogenesis and neurogenesis. We found that susceptibility to developing epilepsy differed in animals housed in complex enriched environments and in those housed in isolated conditions. Kindling epileptogenesis occurred significantly later in animals housed in enriched conditions throughout the procedure (group I) than in animals from groups II and III. We also demonstrated that cells generated during kindling survived for at least 42 days and that these cells were more numerous on both sides of the brain after environmental enrichment than in rats housed in isolated conditions. As similar values were obtained regardless of the duration of the period of enrichment, these cellular changes may not play a major role in delaying kindling development. We suggest that

the increase response in neurogenesis after seizures may be an adaptive rather than epileptogenic response.

COMMENTARY

The literature pertaining to the effect of environmental factors on brain growth and development dates back several decades. In recent years, a large body of research has focused on the beneficial impact of enriched environment on behavioral measures such as memory during senescence and after stroke or trauma, as well as on more fundamental phenomena such as long-term potentiation in the hippocampus and neurogenesis in the dentate gyrus. The interplay between enriched environment and seizures was noted by Young et al. (1), who demonstrated that such experience afforded a measure of protection from kainic acid-induced seizures and also was neuroprotective and inhibited apoptosis.

In the first article highlighted here, Rutten et al., reporting from the laboratory of Dr. Gregory Holmes, show that rats housed in an enriched environment after lithium-pilocarpine status epilepticus (SE) performed substantially better in the Morris water maze, a test of visual-spatial memory, than did rats housed in standard cages. Rats were tested at a series of time points after SE, and the deficits were apparent as early as 2 days after SE and persisted as long as 30 days after SE. Rats that were housed in the enriched environment for 4 weeks after SE demonstrated significantly improved learning during the first 2 days of testing. The authors did not find differences between the two groups in the hilus, CA1, or CA3 in terms of cell counts, nor in the density of Timm granules, a measure of mossy fiber sprouting. Thus the cognitive preservation could not be explained by neuroprotection from delayed cell death, such as may be expected on the basis of the earlier report by Young et al. (1). One might speculate that increased neurogenesis in the dentate may have compensated for some cell loss; such neurogenesis has been reported as a consequence of seizures, as well as of environmental manipulation.

Readers of *Epilepsy Currents*, however, need not speculate on this possibility! A follow-up report from Dr. Holmes' laboratory (2) appeared in a recent issue of *Neurology*, demonstrating just that kind of phenomenon. There is, indeed, increased neurogenesis in animals exposed to the enriched environment, both in the control and SE groups. Both the control and SE rats housed in the enriched environment performed better in the water maze. The authors also found an increase in the transcription factor pCREB. The role of CREB activation in the formation of new memories has been established in species ranging from *Drosophila* to mice. Mice with a targeted mutation in the gene coding for CREB are defective in long-term

potentiation and memory formation. I also recommend the editorial by Drs. Greenwood and Parent (3) accompanying this article for thoughtful reflections on these new findings. They discuss several mechanisms that may play a role in recovery, including "vicariation," in which an adjacent or remote brain region assumes the function of the injured region, and the possibility that neurotrophins may influence dendritic structure and promote increased synaptic efficacy.

These studies highlight the need for important further research in animal models, as well as translational work in the clinical arena. The provision of behavioral stimulation programs for children with brain injury is a costly undertaking that will not be justifiable without strong clinical data supporting their efficacy. Nevertheless, potential long-term economic benefits to society will accrue from minimizing chronic cognitive disability in the affected population. With the appropriate clinical data in hand, it may be possible to convince payers to make such programs available without delay for appropriate candidates when they are most efficacious. Moreover, if the time window in which such environmental manipulation is most beneficial can be determined, cost savings can be achieved by avoiding extending services beyond the time when benefit is likely to be achieved.

Finally, in addition to influencing the degree of behavioral damage caused by seizures, evidence exists that the environment may actually affect the development of epilepsy. Modification of the epileptogenic process has been an important goal of clinicians, and thus far, only discouraging results have been reported for therapeutic measures designed to prevent posttraumatic epilepsy (4). The second article highlighted in this commentary suggests that an enriched environment may modify the epileptogenic process. Auvergne et al. from Bordeaux report on delayed kindling in rats housed in an enriched environment. The benefit was seen only in animals that were placed in an enriched environment before the initiation of amygdala kindling. Animals placed in the enriched environment only during kindling were not significantly different from the control animals in the development of kindling. The authors found neurogenesis to be increased in both groups housed in an enriched environment, but kindling did not have any effect on it; thus neurogenesis may not be a significant factor in epileptogenesis, as was concluded previously by others (5,6). The results from Bordeaux lead to the tantalizing possibility that chronic (and presumably early) exposure to environmental stimulation could have a role in disease prevention in epilepsy, as it has been suspected to afford some measure of protection against dementia. What will be next, red wine?

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