CURRENT LITERATURE

DOES NEUROPROTECTION PREVENT EPILEPTOGENESIS?

Delayed Sclerosis, Neuroprotection, and Limbic Epileptogenesis After Status Epilepticus in the Rat

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PURPOSE: Hippocampal sclerosis and massive neurodegeneration in other parts of the limbic system are considered hallmarks of temporal lobe epilepsy. With the rat model of kainate-induced status epilepticus, we sought to determine if limbic sclerosis after an excitotoxic insult follows a delayed type of neurodegeneration and is thus accessible to neuroprotective intervention after the insult. Effective pharmacologic neuroprotection after status epilepticus also addresses the old question of whether degenerative morphologic changes after an epilepsy-inducing event like status epilepticus are the primary cause of epileptogenesis (i.e., the development of recurrent spontaneous seizures) during the following weeks.

METHODS: Female Wistar rats after 90 minutes of generalized status epilepticus were used. Molecular biologic and histologic techniques were used to demonstrate markers of delayed cell death (apoptosis) 48 hours after the status. The neuroprotective effects of i.c.v. injections of caspase inhibitors and systemic injections of the anticonvulsant drugs (AEDs) dizocilpine and retigabine (RGB) after the status epilepticus were studied. The effect of neuroprotective intervention on the development of recurrent spontaneous seizures was investigated by behavioral observation of the rats.

RESULTS: After generalized status epilepticus in Wistar rats, massive sclerosis of the hippocampus and the piriform cortex occurred. TUNEL labeling and electron microscopy revealed that apoptosis is involved in the degenerative processes. Immunohistochemical analysis of the time course of the expression of the proapoptotic protein Bax suggested a maximal induction of apoptosis 24 to 48 hours after the status. Application of caspase inhibitors before or after the status did not reduce lesions, although Bax labeling was reduced. Injection of dizocilpine and to a lower extent also of RGB after the status prevented limbic neurodegeneration and expression of markers of apoptosis. However, the neuroprotection by dizocilpine did not prevent the development of recurrent spontaneous seizures.

CONCLUSIONS: Prolonged seizure activity can induce delayed sclerosis in the hippocampus and other parts of the limbic system. This delayed cell loss can be prevented by neuroprotective drugs after status epilepticus. However, the damage in limbic brain regions is not the main reason for limbic epileptogenesis and the occurrence of recurrent spontaneous seizures.

COMMENTARY

Several factors relating to the mechanisms of neuronal injury and death may be important in the different forms of injury-induced epilepsy (e.g., temporal lobe and posttraumatic epilepsy). Experimental treatments during or after brain injury that potentially reduce neuronal death are the target of numerous investigations aimed at developing clinical strategies to modify the course of epileptogenesis. Two important questions are (a) Can aggressive neuroprotective therapy *after* a brain injury (e.g., status epilepticus) reduce neuronal loss? and (b) If effective, does such therapy subsequently reduce the development of spontaneous recurrent seizures, and thereby alter the course of chronic epileptogenesis?

The authors provide evidence that treatment with MK-801 or retigabine (RGB) after kainate-induced status epilepticus may reduce lesion volume in the piriform cortex and potentially other limbic areas. The drug-treated animals had slightly smaller lesions than did control animals, but they did not subsequently have fewer chronic seizures (they actually appeared to have more seizures than the controls). In the experiments of Ebert et al., however, only motor seizures were studied, and the total duration of the seizure monitoring was 48 hours. Furthermore, the seizure analysis was performed relatively soon after the status epilepticus (i.e., less than 2 months), when many animals were probably having fewer than one

motor seizure per day. The authors actually reported a mean of one to three motor seizures per animal in the 48 hours of observation. Thus, although the results concerning epileptogenesis were negative, the drug-induced neuroprotection was modest, and the subsequent analysis of chronic seizures was limited in terms of the temporal proximity after the status epilepticus and in the total duration of the seizure monitoring.

The article by Ebert et al. points to the difficulty of this type of research, but additional studies of this nature are necessary if *antiepileptogenic* therapies are to be developed in the future. The experiments focused heavily on the mechanisms of neuronal death after status epilepticus, and a more profound neuroprotective effect from a hypothetical therapy would seem to have a greater chance to generate decisive answers concerning neuron loss and epileptogenesis. The results of this study also highlight the need to design protocols with extensive and appropriately timed monitoring of seizures, which would reduce the possibility of a false-negative outcome. In particular, future studies with substantially increased monitoring of behavioral seizures (and preferably including electrographic recordings) for *several* months after the experimental injury (i.e., well after spontaneous recurrent seizures begin to occur after status epilepticus) may be able to detect hypothetical changes in spontaneous seizure frequency, and thus an alteration in epileptogenesis, even after small but significant neuroprotective effects from experimental therapies.

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