

ROLE OF NEURONAL LOSS IN THE PATHOGENESIS OF RECURRENT SPONTANEOUS SEIZURES

***N*-Methyl-D-aspartate Receptor Blockade after Status Epilepticus Protects against Limbic Brain Damage but Not against Epilepsy in the Kainate Model of Temporal Lobe Epilepsy**

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Most patients with temporal lobe epilepsy (TLE), the most common type of epilepsy, show pronounced loss of neurons in limbic brain regions, including the hippocampus. The massive neurodegeneration in the hippocampus is known as hippocampal sclerosis and is considered one of the hallmarks of this type of difficult-to-treat epilepsy. A long and ongoing debate has considered whether this sclerosis is the result of an initial pathologic event, such as a status epilepticus (SE), stroke or head trauma, which often precedes the development of TLE, or is caused by the spontaneous recurrent seizures (SRSs) once epilepsy has developed. At present, pharmacologic prevention of limbic sclerosis is not available. In a clinical situation, such prevention would be possible only if delayed cell death developing *after* an initial pathologic event is involved. Assuming that sclerotic brain lesions provoke epileptogenesis and that delayed cell death is involved in these lesions, it should be possible to prevent both the lesions and the epilepsy by a prophylactic treatment after an initial insult such as an SE. To test this hypothesis, we used a rat model of TLE in which limbic brain lesions and epilepsy with SRSs develop after a kainate-induced SE. A single low dose of the *N*-methyl-D-aspartate (NMDA)-receptor blocker dizocilpine (MK-801) significantly reduced the damage in limbic regions, including the hippocampus and piriform cortex, and completely protected several rats from such damage when given *after* an SE of 90 minutes induced by kainate, strongly suggesting that delayed cell death is involved in the damage. This was substantiated by the use of molecular and immunohistochemical markers of delayed active (“programmed”) cell death. How-

ever, the neuroprotection by dizocilpine did not prevent the development of SRSs after the SE, suggesting that structures not protected by dizocilpine may play a role in the genesis of SRSs or that epileptogenesis is not the consequence of structural lesions in the limbic system. The only brain regions that exhibited neuronal damage in all rats with SRSs were the hilus of the dentate gyrus and the mediodorsal thalamus, although treatment with dizocilpine reduced the severity of damage in the latter region. The data indicate that NMDA-receptor blockade immediately after a prolonged SE is an effective means to reduce the damage produced by a sustained SE in several brain regions, including the hippocampus, but show that this partial neuroprotection of the limbic system does not prevent the development of epilepsy.

COMMENTARY

A characteristic feature of mesial temporal lobe epilepsy is neuronal loss, which consists of the loss of CA1 and CA3 pyramidal cells and of hilar neurons in the hippocampus. Additional neuronal damage occurs in associated limbic structures, including the amygdala, entorhinal cortex, and dorsomedial thalamus. Early evidence suggested a strong correlation between neuronal loss and recurrent seizures in patients with temporal lobe epilepsy. For instance, electrical stimulation-induced and chemical-based animal models of temporal lobe epilepsy demonstrated a pattern of neuronal loss similar to that observed in human patients. Therefore, researchers hypothesized that neuronal loss is an essential part of the pathogenesis of recurrent spontaneous seizures and that prevention of neuronal loss after an initial neurologic insult, such as prolonged febrile convulsions or head trauma, may protect against development of epilepsy. However, a clear-cut association between the neuronal loss and recurrent seizures increasingly has been called into question.

Growing evidence suggests that temporal lobe epilepsy can develop with minimal neuronal loss. Activation of *N*-methyl-D-aspartate (NMDA) receptors is known to play an important role in producing neuronal loss in experimental models of temporal lobe epilepsy. The noncompetitive

NMDA-receptor antagonists ketamine, phencyclidine, and MK-801 protect against neuronal damage associated with kainic acid-induced and lithium/pilocarpine-induced status epilepticus (1). The current study by Brandt et al. uses the kainate model of temporal lobe epilepsy to demonstrate that the NMDA-receptor antagonist MK-801 protected many neurons—most significantly neurons in the hippocampus, entorhinal cortex, and amygdala. Despite the protection from neuronal loss, recurrent spontaneous seizures developed in the kainite-treated rats.

Earlier studies suggested that the extent and site of neuronal loss in animal models of temporal lobe epilepsy are variable, with some epileptic animals showing minimal cell loss in the hippocampus (2). Patterns of status epilepticus-induced cell loss also are dependent on the state of development of the nervous system (3). For instance, in young animals, status epilepticus appears to cause minimal cell loss and yet leads to development of recurrent spontaneous seizures (4,5). Finally, the extent and site of cell loss also are affected by the method used to induce status epilepticus.

The research by Brandt et al. may be interpreted to suggest that brain damage is not necessary to cause recurrent spontaneous seizures. Alternately, the findings observed in the current study could suggest that subtle neuronal loss in the hip-

pocampal dentate hilus and in the mediodorsal thalamus is the critical, minimal neuronal loss necessary for epileptogenesis. Finally, multiple mechanisms of epileptogenesis may exist, in which some mechanisms require neuronal loss, and others do not. Future experiments with genetic models must resolve whether temporal lobe epilepsy can develop without neuronal loss.

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References

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