

NEUROIMAGING MARKERS OF EPILEPTOGENESIS

Predictive Value of Cortical Injury for the Development of Temporal Lobe Epilepsy in 21-Day-Old Rats: An MRI Approach Using the Lithium-Pilocarpine Model

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PURPOSE: Patients with temporal lobe epilepsy (TLE) usually had an initial precipitating injury in early childhood. However, epilepsy does not develop in all children who have undergone an early insult. As in patients, the consequences of the lithium-pilocarpine-induced status epilepticus (SE) are age dependent, and only a subset of 21-day-old rats will develop epilepsy. Thus with magnetic resonance imaging (MRI), we explored the differences in the evolution of lesions in these two populations of rats.

METHODS: SE was induced in 21-day-old rats by the injection of lithium and pilocarpine. T₂-weighted images and T₂ relaxation-time measurements were used for detection of lesions from 6 hours to 4 months after SE.

RESULTS:

Three populations of rats could be distinguished. The first one had neither MRI anomalies nor modification of the T₂ relaxation time, and these rats did not develop epilepsy. In the second one, a hypersignal appeared at the level of the piriform and entorhinal cortices 24 hours after SE (increase of 49% of the T₂ relaxation time in the piriform cortex) that began to disappear 48 to 72 hours after SE; epilepsy developed in all these animals. The third population of rats showed a more moderate increase of the T₂ relaxation time in cortices (14% in the piriform cortex) that could not be seen on T₂-weighted images. Epilepsy developed in all these rats. Only in a subpopulation of the 21-day-old rats with epilepsy did hippocampal sclerosis develop.

CONCLUSIONS: These results suggest that the injury of the piriform and entorhinal cortices during SE plays a critical role for the installation of the epileptic networks and the development of epilepsy.

COMMENTARY

The development of chronic epilepsy after a precipitating injury is often associated with a delay or “latent period” of weeks to several years (1). During the latent period, there is progressive axonal and dendritic plasticity, significant neuronal death, marked gliosis, and molecular reorganization of receptors and ion channels. Collectively, these and other neurobiologic changes are thought to contribute to increased network hyperexcitability and ultimately to the expression of clinical seizures. The latent period provides a “window of opportunity” for intervention with novel therapies aimed at preventing the development of epilepsy. Such antiepileptogenic therapies may be entirely different from those that are effective in the symptomatic treatment of seizures associated with chronic epilepsy. The process currently used in the search for new antiepileptic drugs (AEDs) uses normal rodents and acute seizure models (e.g., maximal electroshock and subcutaneous pentylene-tetrazol). Subsequent testing often involves evaluating a new therapeutic drug in the kindled rat model of partial epilepsy. Historically, this approach has been very successful for identifying new AEDs for the symptomatic treatment of epilepsy; however, it is not likely to identify a substance that will slow, halt, or prevent epilepsy development. Chronic models could be used in the search for antiepileptogenic agents, but approaches are needed to follow the epileptogenic process. The present study by Roch et al., wherein they demonstrate that lesions detected in the piriform and entorhinal cortices by magnetic resonance imaging (MRI) predict the development of chronic epilepsy, suggests that it may be possible to detect a “disease modifying” therapeutic effect early in the course of treatment by using sophisticated imaging methods. This approach, if validated, could dramatically enhance our opportunity to identify the truly novel AED.

In recent years, significant effort has been devoted to the development of animal models that more closely reflect the pathophysiology and phenotypic features of human epilepsy (2). Of the various epilepsies and epilepsy syndromes, the acquired epilepsies account for ~30% of new cases and are perhaps the easiest to model at the present time. The probability of developing epilepsy after acute status epilepticus is reasonably high and by some estimates can reach 40% (3). Status epilepticus can be induced in animals by a number of different

stimuli including electrical stimulation of limbic brain structures and systemic or local injection of the chemoconvulsants kainic acid, pilocarpine, and lithium-pilocarpine. Unlike humans, in a large proportion of adult animals that survive the initial status epilepticus, spontaneous seizures develop after a latent period of several days to weeks. The ensuing damage to the brain after acute status is similar to that seen in human mesial temporal lobe epilepsy and includes marked neuronal cell loss, gliosis, axonal sprouting, and neurogenesis. The incidence of chronic epilepsy is reduced in 21-day-old (P21) rats after acute status epilepticus. Because not all P21 rats will develop epilepsy after status epilepticus, the immature rat provides a useful platform to identify factors associated with the development of enhanced seizure susceptibility.

In the present study, Roch et al. used MRI to evaluate the evolution of lesions in epileptic and nonepileptic rats after lithium-pilocarpine-induced status epilepticus. Status epilepticus was induced at P21, and lesion development was followed with MRI from 6 hours to 4 months after the initial insult. Three populations of rats were identified. In the first (17% of survivors), epilepsy did not develop, nor could any MRI abnormalities be identified. In the second (37% of survivors), chronic epilepsy was associated with visible MRI abnormalities in the piriform and entorhinal cortices. In the third (46% of survivors), epilepsy was associated with an increase of T_2 relaxation time in the piriform and entorhinal cortices but with no visible MRI abnormalities in these or other limbic structures evaluated. Overall, the results support the hypothesis that injury to the piriform and entorhinal cortices during status epilepticus plays a critical role in the subsequent development of chronic epilepsy.

In this study, it is noteworthy that detectable changes in T_2 relaxation times in the piriform cortex (and less so in the entorhinal cortex) could be observed as early as 24 hours after

status epilepticus in those rats in which epilepsy ultimately developed. The ability of MRI to reliably predict clinical outcome early after an insult would provide a powerful experimental tool to assess the efficacy of novel therapeutic agents designed to prevent or modify the development of epilepsy. Clearly, additional studies are required to confirm these findings in other epileptogenesis models and to assess whether early intervention with a therapy that prevents detectable shifts in T_2 relaxation times is also associated with disease modification. Nonetheless, coupling MRI or other predictive techniques to clinical outcome in early preclinical studies could represent a useful experimental approach for identifying those therapies that prevent or modify the development of epilepsy.

Given recent advances at the molecular and genetic level and developments in seizure prediction and brain imaging, a “cure” (or at least the prevention) of some forms of acquired epilepsy would appear to be a reasonable expectation for the not-so-distant future. One challenge will be to develop preclinical model systems that can be used in early proof-of-concept studies that ultimately support more timely and costly human studies. The present report by Roch et al. suggests that we may be getting close.

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References

1. Walker MC, White HS, Sander JW. Disease modification in partial epilepsy. *Brain* 2002;125:1937–1950.
2. White HS. Animal models of epileptogenesis. *Neurology* 2002;59(9 suppl 5):S7–S14.
3. Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Risk of unprovoked seizure after acute symptomatic seizure: effect of status epilepticus. *Ann Neurol* 1998;44:908–912.