

EXCITATORY AFFERENTS TO THE ENTORHINAL CORTEX PLAY A ROLE IN TEMPORAL LOBE EPILEPTOGENESIS

Ibotenate Injections into the Pre- and Parasubiculum Provide Partial Protection Against Kainate-Induced Epileptic Damage in Layer III of Rat Entorhinal Cortex

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PURPOSE: A loss of neurons in layer III of the entorhinal cortex (EC) is often observed in patients with temporal lobe epilepsy and in animal models of the disorder. We hypothesized that the susceptibility of layer III of the EC to prolonged seizure activity might be mediated by excitatory afferents originating in the presubiculum.

METHODS: Experiments were designed to ablate the presubiculum unilaterally by focal ibotenate injections and to evaluate the effect of this deafferentation on the vulnerability of EC layer III neurons to the chemoconvulsant kainate (injected systemically 5 days later).

RESULTS: After treatment with kainate, 11 of the 15 rats preinjected with ibotenate showed clear-cut, partial neuroprotection in layer III of the EC ipsilateral to the ibotenate lesion. Serial reconstruction of the ibotenate-induced primary lesion revealed that entorhinal neurons were protected only in animals that had lesions in the pre- and parasubiculum, especially in the deep layers (IV–VI).

CONCLUSIONS: The deep layers of the pre- and parasubiculum appear to control the seizure-induced damage of EC layer III. This phenomenon may be of relevance for epileptogenesis and for the pathogenesis of temporal lobe epilepsy.

III of medial entorhinal cortex often identified in pathological samples from patients who have undergone epilepsy surgery. The pattern of damage seen is similar to that which develops in several animal models of epilepsy, including those involving the administration of excitotoxins. Lesions in layer III of entorhinal cortex are thought to give rise to hyperexcitability in hippocampus, manifested as seizures. Such lesions can be prevented by agents that antagonize N-methyl-D-aspartate (NMDA)-mediated transmission, underscoring the likely role for excitotoxicity in effecting this damage to layer III. Given that the excitotoxic process is a downstream event from the excessive discharge of major excitatory (glutamatergic) afferents onto a vulnerable structure and that destroying or otherwise blocking this transmission successfully aborts this process, the authors hypothesized that eliminating the major input to layer III, specifically the presubiculum and parasubiculum, would, in turn, protect layer III cells.

The study used a chemical ablation technique with ibotenate to remove areas in the parahippocampal region and then challenged animals with a systemic injection of kainate that reliably produces status epilepticus and bilateral degeneration of layer III of the entorhinal cortex. Although the lesions did not prevent the kainate-induced status epilepticus, it did partially protect ipsilateral layer III neurons in the medial entorhinal cortex in 11 of 15 animals. The consistent finding in all of the animals showing protection against kainate-induced neuronal loss was the presence of an ibotenate-induced lesion in the deep layers (IV–VI) of the presubiculum and parasubiculum. In the four animals that did not show protection, the presubiculum/parasubiculum was intact. Taken together, this is rather conclusive evidence for the role of this brain region in the excitotoxic damage, which ensues in medial entorhinal cortex layer III following vigorous seizure activity. This simple result is obviously the consequence of rather complex processes, involving as yet undefined circuit interactions within and between the hippocampus and various parahippocampal structures.

Issues that were not addressed in this study are the potential effects of removal of presubiculum/parasubiculum upon acute seizures and the development of chronic epilepsy. The acute kainate-induced convulsive status epilepticus was similar

COMMENTARY

The entorhinal cortex, which gives rise to the perforant path projection to the hippocampus, plays an important, albeit mysterious role in the pathophysiology of temporal lobe epilepsy. Lesions in the entorhinal cortex are known to occur in temporal lobe epilepsy patients, with degeneration in layer

in the lesion and control groups, but because electrical recordings were not performed, possible electrographic differences between groups could not be assessed. There is the implication that entorhinal neuroprotection might prevent the development of late spontaneous seizures, progressive memory impairment, and hippocampal damage, as it is envisioned that damage to layer III is the first step in a cascade of events leading to these outcomes. Nonetheless, this is by no means a certainty. A

cause and effect relationship has yet to be defined here, and the attendant damage to layer III may be an epiphenomenon within the whole scheme. Regardless, the important point here is that it is possible to protect against excitotoxic damage by disconnecting an offending afferent system from its vulnerable neuronal targets.

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