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MECHANISMS OF SEIZURE SUSCEPTIBILITY AND EPILEPTOGENESIS

Cell death after single and repeated brief seizures

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Summary

We review the experimental evidence from animal models that suggest that brief, evoked seizures can result in neuronal death while spontaneous seizures normally do not, as well as human data showing damage may progress in certain patients, and we describe the cell death and survival pathways regulating these processes. For an expanded treatment of this topic see *Jasper's Basic Mechanisms of the Epilepsies, Fourth Edition* (Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AC, eds) published by Oxford University Press (available on the National Library of Medicine Bookshelf [NCBI] at www.ncbi.nlm.nih.gov/books).

KEY WORDS: Apoptosis, Bcl-2, Caspases, Cell death signalling, DNA fragmentation, Epilepsy, Excitotoxicity.

The question of whether single or repeated brief seizures cause cell death is germane to both clinicians and experimentalists, and remains controversial. In this chapter the authors review the cell death and survival mechanisms after single and repeated brief seizures.

Repeated brief seizures in animals, for example, evoked by electrical stimulation of the perforant path or hippocampus, can result in neuronal death. There is also evidence that once injury breaches a threshold, spontaneous seizures can emerge. However, the extent of cell loss displays intermodel variability and in some cases has been overestimated (Sutula et al., 2003).

There has been less compelling evidence that spontaneous (epileptic) seizures in animal models cause neuronal death, and temporal lobe structures are not more damaged in animals experiencing more frequent seizures. However, in addition to certain pathology data there is neuroimaging evidence from patients with poorly controlled temporal lobe epilepsy that supports small progressive declines in tissue volume in hippocampus and perhaps extrahippocampal structures (Duncan, 2002).

A mixture of excitotoxic and programmed (apoptotic) mechanisms may be involved in cell death after brief seizures. Damaged cells stain for irreversible DNA fragmentation and some display morphologic features consistent with apoptosis, although the cell death signaling pathways remain less-well researched than those activated after status epilepticus. Evidence of apoptosis-associated signaling has been reported in refractory human temporal lobe epilepsy, including select regulation of Bcl-2 family proteins, stress pathways, caspases, and downstream substrates (Rocha et al., 2007).

In summary, animal data point to cell death as a consequence of repeated evoked brief seizures, but query whether spontaneous seizures contribute to further neuronal loss. Human data suggest neuronal loss may occur in some patients with poorly controlled epilepsy and apoptosis-associated signaling pathways may contribute to the underlying mechanisms.

Disclosure

The authors declare no conflicts of interest.

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