Neuroprotection and antiepileptogenesis

Overview, definitions, and context

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The stated goal of the community of physicians and scientists who treat and study epilepsy, as articulated at an NIH-sponsored consensus conference in 2000, is "no seizures, no side effects." The conference report, however, makes clear that suppression of the symptoms of epilepsy, i.e., seizures per se, is not sufficient. Additional efforts must focus on preventing the development of epilepsy in individuals at risk and preventing the negative consequences of seizures when they occur (see http://www.ninds.nih.gov/about_ninds/epilepsybenchmarks.htm). This holistic approach to epilepsy, which emphasizes disease modification in addition to symptomatic relief, represents nothing less than a paradigm shift for the discoverers, developers, prescribers, and users of epilepsy therapeutics.

Gowers recognized that "seizures beget seizures" over a century ago. Using the tools of clinical observation alone, however, it was impossible to determine whether seizures were epileptogenic or whether both the initial seizure and subsequent seizures a patient experienced were the result of a common pathology or genetic predisposition. Recent studies using animal models strongly support the notion that an otherwise normal individual can develop epilepsy as the result of an initial seizure.[1,2] These studies used chemoconvulsants to induce status epilepticus and then documented the occurrence or spontaneous recurrent seizures weeks to months later. It remains unclear whether a single seizure or nonconvulsive seizures have the same potential to induce epilepsy in otherwise normal individuals.

As early as 1825, Bouchet and Cazauvielh[3] noted loss of neurons in the hippocampus of patients with seizures. Subsequent studies of autopsy material and surgical specimens have amply supported the notion that there is a specific topography of neuronal loss in patients with certain types of epilepsy and that there are additional pathological markers of brain injury in these patients, including atrophy, gliosis, reactive astrocytes, and microglial proliferation. Despite the overwhelming evidence for anatomic injury in patients with epilepsy, it has been much more difficult to establish whether seizures are the cause or the consequence, or perhaps both. Here, too, animal models have improved our understanding of the relationship between seizures and injury. Normal animals exposed to status epilepticus develop a stereotyped pattern of cell loss and gliosis,[4–6] supporting the notion that seizures cause injury. By contrast, animals with focal lesions, such as cortical dysplasia or migrational abnormalities, manifest clinical seizures infrequently,[7,8] making the notion that injury causes seizures more difficult to prove. Moreover, it appears likely that some kinds of seizures, such as absence and benign rolandic seizures, may occur repeatedly without causing overt injury.

The preceding discussion highlights the two important concepts that form the subject matter of this supplement, seizure-induced injury and epileptogenesis. With the recent development of a host of new antiepileptic drugs, considerable interest has focused around the question of whether any or all of these compounds might have disease-modifying activities. An important limitation of work in this field is that most studies have addressed the neuroprotective and antiepileptogenic activities of existing antiepileptic drugs rather than taking a broader approach to examining drugs from other classes for neuroprotective or antiepileptogenic activity. Therefore, this supplement specifically considers the question of whether we have drugs with neuroprotective or antiepileptogenic properties, in addition to their demonstrated antiepileptic properties.

Definitions. *Antiepileptic.* An antiepileptic compound prevents or reduces epileptic seizures. Because not all seizures are convulsive, this term is preferred to anticonvulsant.

Neuroprotective. A compound with neuroprotective activity prevents neuronal injury. An antiepileptic may be neuroprotective if seizures are injurious

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or if the compound has an additional protective activity independent of its antiepileptic activity.

Antiepileptogenic. An antiepileptogenic compound prevents or slows the process of developing epilepsy. An antiepileptic might be antiepileptogenic if the seizures it blocks are themselves epileptogenic. A neuroprotective compound might be antiepileptogenic if injury leads to epilepsy. Alternatively, some compounds might have antiepileptogenic activity without either blocking seizures or preventing injury.

Context. Behavioral, anatomic, biochemical, and molecular techniques have revealed an extraordinary range of responses of the previously normal brain to brief episodes of abnormal activity such as that seen during epileptic seizures. Calcium ion influx, gene activation and expression, kinase activation, cell loss, synaptic remodeling, neurogenesis, behavioral change, and enhanced susceptibility to additional seizures have all been described (see Cole[9] for review). These events occur on a timescale from milliseconds to months. If one hypothesizes that seizures are either epileptogenic or injurious, it appears likely that some of the short-term consequences of seizures act to transduce brief episodes of abnormal neuronal activity into long-term functional and anatomic changes in the CNS. This process, which is temporally dispersed, offers a therapeutic target for agents that are antiepileptogenic or neuroprotective. It remains unclear whether the transduction process is arranged in a linear series fashion or whether multiple short-term processes lead in parallel to the same long-term result. An answer to this question has obvious implications for the development of neuroprotective and antiepileptic therapeutics.

This supplement has been developed to address the issues surrounding neuroprotection and antiepileptogenesis. It is organized to consider and review data from animal and human studies addressing the following questions:

- **Do seizures cause neuronal injury?** Dr. Holmes reviews animal data supporting the idea that seizures cause injury. Dr. Duncan, using mainly neuroimaging data, addresses the issue of whether seizures cause injury in humans.
- **Are seizures epileptogenic?** Dr. White reviews animal models and data addressing the issue of whether seizures are epileptogenic. Dr. Hermann, using mainly epidemiologic data, then considers the question of whether seizures are epileptogenic in humans.
- **Do we have neuroprotective or antiepileptogenic drugs?** Dr. Pitkanen reviews the experimental data from animal studies concerning neuroprotective and antiepileptogenic activity of existing compounds. Dr. Schachter then examines the data, or lack of same, in human studies and outlines strategies for testing the hypothesis that some compounds are neuroprotective or antiepileptogenic in humans.

Although the notions of neuroprotection and antiepileptogenesis are frequently discussed, only recently have investigators taken on the issues in a focused and formal manner. We hope that this supplement will clarify the issues and the terminology in the field, present the best data available, and highlight future directions in the field that will ultimately lead to the stated goal of a cure for epilepsy, i.e., "no seizures, no side effects."

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