



Editorial

New strategies for preventing epileptogenesis: Perspective and overview

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ABSTRACT

Epilepsy is a common disorder with a major negative impact on patient quality of life, yet treatment so far is directed mainly at blocking the symptoms—epileptic seizures, not the underlying cause. In recent years, investigation of epilepsy development or epileptogenesis has yielded new insights into potential therapies that may ultimately prevent epilepsy before it starts. In this special issue of *Neuroscience Letters* the latest advances in the field are brought together, summarizing: (1) important animal models in both primary and secondary epilepsies, (2) promising biomarkers for monitoring epileptogenesis, (3) cellular and molecular mechanisms which may serve as viable targets for therapy, and (4) translational approaches to human clinical trials. Bringing together these intriguing new approaches to treating epilepsy as a preventable disorder will hopefully soon make symptomatic treatment of epilepsy unnecessary in most patients.

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Epilepsy is the most common chronic neurological disorder and has an enormous impact on lifelong function. Interestingly, there is usually a period of time before the onset of epilepsy which may provide an opportunity for early intervention. In both primary genetically determined epilepsy and secondary epilepsy following a brain insult there is typically a latent period before epileptic seizures become fully manifest. The term “epileptogenesis” refers to the biological changes that lead to the development of recurrent spontaneous seizures in epilepsy. Until recently, this process was considered inevitable and most epilepsy treatments focused on treating seizures symptomatically, or to stopping seizures after the epileptic condition has already developed. Exciting new findings in the past decade for the first time make “anti-epileptogenesis” a real possibility, so that the goal of primary prevention of epilepsy may soon come into reality.

In this special issue of *Neuroscience Letters*, many of the important findings in the rapidly evolving field of anti-epileptogenesis are summarized by investigators doing this crucial work. The emphasis of the articles is on new strategies and paradigms for preventing epileptogenesis. Because we have focused here on novel therapies and mechanisms, many of the results in this issue come from animal models, although the translational value to human patients is constantly increasing.

The initial articles in this issue describe several important animal models for studying epileptogenesis and its prevention. McClelland et al. present novel findings from an animal model of epileptogenesis following prolonged febrile seizures, an important and common condition seen in human patients [8]. Traumatic brain injury, another common cause of human epilepsy is next discussed through cutting-edge studies in animal models both *in vivo* by Pitkänen et al. [11] and *in vitro* by Li et al. [5].

Somewhat surprisingly, the most promising evidence to date showing the effectiveness of therapy in preventing epileptogenesis

comes from models of genetically determined primary generalized epilepsy. These models are introduced by van Luijckelaar [14]. The benefits of early treatment in preventing both epilepsy and psychiatric co-morbidities, and the persistence of these beneficial effects even after treatment is stopped is discussed further by van Luijckelaar, as well in the articles by Jones et al. and by Mishra et al. [14,3,10]. These latter two articles introduce the next topic, which is the search for effective biomarkers for monitoring changes in the brain related to epileptogenesis as well as any beneficial effects of treatment, focusing on neuroimaging methods including morphometric analysis, diffusion tensor imaging, resting functional connectivity and other techniques. Recognizing the changes that occur during epileptogenesis using non-invasive biomarkers will ultimately be crucial for designing human treatment trials, so additional approaches are discussed using systems biology by Loeb [6] and using peripheral blood microarray studies by Karsten et al. [4].

The next articles review some important cellular and molecular mechanisms of epileptogenesis which may serve as viable targets for therapy. These include changes in GABA receptors as presented by González and Brooks-Kayal [2], inflammatory mechanisms as discussed by Ravizza et al. [12], and signaling changes mediated by the mammalian target of rapamycin (mTOR) reviewed by McDaniel and Wong [9]. In addition, as described by Dudek and Staley, recent studies suggest that epileptogenesis begins shortly after brain injury and continues progressively even after seizures have begun [1]. As Staley, White and Dudek further point out, epileptogenesis may depend critically on cumulative activity-dependent plasticity produced by repeated epileptiform discharges in the form of interictal spikes [13]. *If interictal spikes are mechanistically important, this may explain why antiepileptic medications have so far shown very promising anti-epileptogenic effects only in primary generalized but not in secondary epilepsies.* This difference in anti-epileptogenic effects may be related to the fact that antiepileptic medications

block interictal epileptic spikes effectively in primary generalized but not in secondary epilepsy.

The final article by Mani, Pollard and Dichter bring these results directly into the clinical arena by describing how effective human clinical trials will best be carried out—hopefully in the near future—to prevent epileptogenesis [7].

The articles in this special issue span a wide range of techniques and levels of investigation reflecting the diverse approaches currently being taken in this field all converging on the same ultimate goal. It should be noted that although an effort was made to be as inclusive as possible, of course there are additional topics which have been omitted, and for this apologies are in order. In addition, the rapid pace of this research may make some topics obsolete nearly as quickly as these review articles can be published. Nevertheless, it is hoped that this collection of articles will help inform those interested in anti-epileptogenesis, and will inspire additional novel approaches that will soon make epilepsy a preventable disorder.

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Guest Editor

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