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Epileptogenesis, Traumatic Brain Injury, and Biomarkers

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Abstract

Epilepsy is one of the most common brain disorders, causing serious disability and premature death worldwide. Approximately 1.2% of the U.S. population has active epilepsy, and 30 to 40% have seizures that do not respond to antiseizure drugs. There currently is no treatment available that prevents epilepsy following a potential epileptogenic insult, and the search for disease or syndrome modifying interventions for epilepsy is a high priority of neurobiological research. This requires better understanding of neuronal mechanisms underlying the development of epilepsy, and biomarkers of this process that would permit cost-effective drug discovery, and validation in clinical trials, for potential antiepileptogenic compounds. EpiBioS4Rx is an NIH-funded Center without Walls consisting of collaborative investigations in the United States, Europe, and Australia of traumatic brain injury in patients, and a standardized animal model, to identify biomarkers of epileptogenesis and to determine their ability to assess the effectiveness of potential antiepileptogenic agents. Successful completion of this project is expected to result in design of an economically feasible, full-scale clinical trial of at least one antiepileptogenic intervention.

Keywords

Epilepsy; Epileptogenesis; Antiepileptogenesis; Traumatic brain injury; Biomarkers

Introduction

Epilepsy is one of the most common severe diseases of the brain. The chances of experiencing one epileptic seizure in a lifetime is 10%, and one-third of people who experience a single seizure will go on to have recurrent seizures, warranting a diagnosis of epilepsy (1). Although approximately 1% of the world's population have been assumed to have active epilepsy, a recent study by the U.S. Center for Disease Control and Prevention found that the prevalence in the U.S. is 1.2%, considerably higher than previously believed (2). Despite the introduction of 20 new antiseizure medications in the past few decades, 30- to 40% of people with epilepsy are pharmacoresistant (3), meaning they continue to have

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Competing Interests

The author has no competing interests.

disabling seizures with appropriate medical treatment. Drug resistant epilepsy (DRE) accounts for 80% of the cost of this disease in the industrialized world (4). It is estimated that 80% of people with epilepsy live in developing countries, where they receive inadequate treatment or no treatment at all (5). Physical, psychological, and social morbidity associated with drug-resistant epilepsy is high, and the mortality rate is five to ten times that of the general population (6). In industrialized countries, 80% of the cost of epilepsy is attributed to drug resistance (4). According to the World Health Organization, epilepsy accounts for 1% of the global burden of disease, calculated as disability-adjusted life years (DALYs), the number of life years lost due to disability or premature death (7). This is equivalent to breast cancer in women and to lung cancer in men. Among primary diseases of the brain, this is equivalent to depression, to dementia, and to substance abuse. It is now recognized that the figure for epilepsy is, in fact, a gross underestimate because when epilepsy was caused another condition, such as trauma, stroke, or a brain tumor, it was listed in this survey as the other condition and not epilepsy. It is noteworthy that the media attention and resources devoted to epilepsy are significantly less than those devoted to other diseases that pose a similar burden, in part because epilepsy has been a stigmatized disorder, since biblical times. This stigma has not only left epilepsy in the shadows, but has contributed greatly to the psychological and social disability experienced by people with epilepsy.

Epilepsy

Although epilepsy is regarded as a disease, epileptic seizures are symptoms of many different diseases, and there are, therefore, many different types of epilepsy. A simplistic view is that the nervous system has a limited repertoire of responses to noxious insult – it can underact, producing negative symptoms such as paralysis or blindness, or it can overact, producing positive symptoms such as pain, the most common positive symptom of the peripheral nervous system, or epileptic seizures, the most common positive symptom of the central nervous system. Any abnormality that irritates the brain can cause epileptic seizures. Epilepsy can be divided into conditions caused directly by genetic mutations, so-called epilepsy genes, or by structural or metabolic abnormalities (8). The latter are more common and consist of disturbances such as brain trauma, cerebral infections, vascular accidents, brain tumors and malformations of brain development. As a result of modern diagnostic advances in neuroimaging and electroencephalography (EEG), the underlying structural causes of epilepsy can be diagnosed in most patients. Nevertheless, there is no treatment to prevent epilepsy, nor to cure it other than with surgical removal of a discrete epileptogenic lesion. A priority area of research in the field of epilepsy is to develop effective approaches for prevention, with the hope that this may also lead to approaches to cure.

Epileptogenesis

The term *epileptogenesis* refers to the structural and functional changes that occur, following a potential epileptogenic insult, which ultimately lead to the appearance of spontaneous epileptic seizures (9). The period of epileptogenesis between insult and the manifestation of epilepsy is referred to as the *latent period*. Epileptogenesis also refers to the progression of epileptic signs and symptoms in some forms of epilepsy, after the initial seizures occur (9). Research aimed at identifying approaches to prevent epilepsy begin with studies to identify

the fundamental neuronal mechanisms of epileptogenesis in different types of epilepsy, and then to devise interventions that abort or reverse this process, referred to as *antiepileptogenesis* (9). Antiepileptogenesis can lead to complete prevention which stops the development of epilepsy, or partial prevention which delays the development of epilepsy or reduces its severity. Antiepileptogenesis can also prevent or reduce the progression of epilepsy after it has already been established. The term *disease or syndrome modification* is used to refer to both antiepileptogenesis, and *co-morbidity modification* when treatment alleviates or reverses the symptomatic development or progression of epilepsy-related co-morbidities such as anxiety, depression, somato-motor impairment, or cognitive decline (9).

The most common structural abnormality resulting in pharmacoresistant human epilepsy is hippocampal sclerosis, which is the pathophysiological substrate for most patients with the condition known as mesial temporal lobe epilepsy (MTLE) (10). For this reason, many well-defined animal models of MTLE with hippocampal sclerosis have been developed for research purposes, and parallel animal/human studies that utilize data acquired from patients with MTLE who undergo resective surgical treatment, have elucidated epileptogenic disturbances at levels from the channel and membrane to systems involving the whole brain (11). Human studies have produced a partial understanding of the endpoint of the epileptogenic mechanism that results in the generation of spontaneous seizures in this condition. Although studies of epileptogenesis have also been carried out during the latent period in experimental animal models of MTLE, these are not possible in human subject populations because patients do not come to the attention of physicians until after seizures have occurred. Investigations into epileptogenesis, and ultimately antiepileptogenesis, in humans, require a common condition in which the latent period can be monitored, that means a condition where the timing of the initial epileptogenic insult is known. Ideally, this should also be a condition that can be modeled in the animal laboratory.

Translational studies of epileptogenesis

Epileptogenic mechanisms can be investigated during the latent period in several forms of acquired human epilepsy, the most often encountered being posttraumatic epilepsy (PTE) following traumatic brain injury (TBI). Other conditions include epilepsy that occurs following stroke or other vascular accidents, tuberous sclerosis complex (TSc), and epilepsy associated with neurocysticercosis (NCC). Because PTE is the most common of these, it is the most amenable to large-scale investigations. TBI occurs in all industrialized countries where basic neuroscience research is carried out, and 15- to 25% of patients with moderate to severe TBI develop PTE (12). Several excellent animal models of PTE have been developed, and the most active research using parallel animal/human paradigms for translational studies of epileptogenesis are now being carried out on TBI (13).

Two to 4% of individuals experiencing cerebral vascular accidents will develop epilepsy, especially those with hemorrhagic and embolic strokes (14). Some animal models of post stroke epilepsy have been created and there is a potential to develop parallel animal/human investigations into epileptogenesis in this condition (15).

Considerable work is being carried out to elucidate the molecular basis of TSc, which can usually be diagnosed at birth (16). Because most children with TSc develop epilepsy within the first year of life, this theoretically provides an opportunity to investigate epileptogenic mechanisms over a relatively short period of time in a high percentage of subjects. Animal models of TSc exist for translational study paradigms (17). One problem with studies of this condition, however, is that it is not clear whether changes occurring in the first year after birth represent epileptogenesis, or whether the epileptogenic changes occurred prior to birth, and delay to first seizure onset merely reflects the normal brain maturation required to support clinical manifestations.

Neurocysticercosis is the most common cause of epileptic seizures in endemic areas, which include Latin America, much of Southeast Asia, and parts of West Africa (18). Patients with NCC can also develop recurrent seizures, but it is not always clear whether this represents a true epileptogenic abnormality or recurrent inflammatory changes in the cyst (18). An interesting recent observation is that when patients with pharmacoresistant epilepsy due to NCC are evaluated for surgical treatment, seizures often originate in hippocampus and not in the cyst (19). It seems likely, therefore, that NCC can promote hippocampal sclerosis and MTLE, creating a situation where it may be possible to study epileptogenic mechanisms of MTLE before chronic seizures occur (18).

Biomarkers

Although TBI leading to PTE provides the best opportunity for investigating epileptogenesis using a parallel animal/human research paradigm, it would not be economically feasible, under current conditions, to carry out clinical trials of TBI subjects to validate potential antiepileptogenic interventions. As only 15- to 25% of patients undergoing moderate to severe TBI develop PTE, and seizures can begin years after injury, clinical trials would need to involve extremely large subject populations followed for long periods of time, making them prohibitively expensive (20). Consequently, research into fundamental mechanisms of epileptogenesis following TBI is also directed at identifying biomarkers of epileptogenesis (20–23). Biomarkers that could reliably indicate a high likelihood of developing PTE following TBI would permit enrichment of the subject population. Biomarkers that could indicate the existence of an epileptogenic process would make it possible to determine the effectiveness of an intervention to eliminate epileptogenic potential without the need to wait for epileptic seizures to occur. Biomarkers might stage the epileptogenic process, suggesting the need for different types of interventions at different times following injury. Biomarkers might also make it possible to monitor the progress of epileptogenesis and, therefore, the effects of an antiepileptogenic intervention over time. Identification of reliable biomarkers to diagnose epileptogenesis would not only enable clinical trials of potential antiepileptogenic treatments, but might facilitate the discovery of antiepileptogenic agents by permitting the development of cost-effective rapid-throughput models to screen for candidate compounds. Finally, the search for biomarkers could yield targets for novel antiepileptogenic drugs.

Much work has been published in recent years on putative imaging, electrophysiological, molecular, and cellular biomarkers of epileptogenesis following TBI (20–23). Predictive power will likely require a combination of electrophysiological, neuroimaging, and

molecular biomarkers measured at different post-injury time points, to diagnose with high sensitivity and specificity ongoing epileptogenesis independent of the severity of brain damage. A primary obstacle in identifying a profile of biomarkers that could be used clinically to facilitate the identification and validation of antiepileptogenic interventions has been the fact that both animal and clinical studies have invariably been underpowered. Furthermore, the lack of standardized approaches has prevented definitive comparative and translational analyses among published studies. For these reasons, the National Institute of Neurological Disorders and Stroke (NINDS) recently funded the Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx; U54 NS100064), a collaborative multicenter, international research investigation of epileptogenesis following TBI.

EpiBioS4Rx

EpiBioS4Rx is an NIH-funded Center Without Walls involving seven principal investigators and multiple primary study sites at the University of California, Los Angeles (J. Engel, Project Director; P. Vespa, Co-PI), the University of Southern California (A. Toga, Corresponding PI), Albert Einstein College of Medicine (S. Moshé, Co-PI; A. Galanopoulou, Co-PI), the University of Eastern Finland (A. Pitkänen, Co-PI), and Monash University (T. O'Brien, Co-PI), as well as 13 Traumatic Brain Injury Centers in the United States, the United Kingdom, Australia, and Russia. This research project is designed to facilitate the identification of biomarkers of epileptogenesis, and the development of antiepileptogenic therapies, by removing barriers and promoting large-scale collaborative investigative efforts involving multidisciplinary teams of basic and clinical neuroscientists with access to extensive patient populations, well-defined and rigidly standardized animal models, and cutting-edge analytic methodology. The research is focused on antiepileptogenesis in posttraumatic epilepsy (PTE) following traumatic brain injury (TBI), as this condition offers the best opportunity to determine the onset of the epileptogenic process in patients.

The EpiBioS4Rx scientific premise is: epileptogenesis after TBI can be prevented with specific treatments; the identification of relevant biomarkers and performance of rigorous preclinical trials will permit the future design and performance of economically feasible full-scale clinical trials of antiepileptogenic therapies (Figure 1). The objectives of this work are to 1) identify biomarkers of epileptogenesis in animal models and patients; 2) develop and utilize a standardized platform for preclinical trials of potential antiepileptogenic drugs; 3) identify one or more lead antiepileptogenic drugs for a future interventional clinical trial; 4) establish a network of advanced TBI centers capable of carrying out future clinical trials featuring the lead antiepileptogenic drugs in the context of a personalized medicine approach, utilizing a panel of biomarkers; and 5) develop and incorporate a public engagement program involving the mutual education and collaboration of consumers, consumer organizations, and professionals to design and execute future large-scale international clinical trials of antiepileptogenic therapies. It is anticipated that research carried out by EpiBioS4Rx investigators will also elucidate fundamental neuronal mechanisms of epileptogenesis and lead to identification of novel targets for disease prevention and modification.

To accomplish these objectives, EpiBioS4Rx is organized into three Cores for administration (Engel/Toga), informatics and analytics (Toga), and public engagement (Moshé), and three Research Projects, for identification of animal biomarkers (Pitkänen), preclinical antiepileptogenic trials utilizing identified biomarkers (Galanopoulou), and identification of biomarkers in patients (Vespa) (Figure 2).

The work of EpiBioS4Rx will result in the creation of open shared resources for the entire epilepsy research community, including an epilepsy-specific bioinformatics platform and database, a robust animal model of TBI leading to PTE, and a standardized preclinical protocol for the evaluation of novel antiepileptogenic therapies. Research carried out during the five year tenure of EpiBioS4Rx is expected to yield one or more candidate antiepileptogenic treatments, as well as biomarker information, resources, expertise, and patient populations sufficient to carry out an economically feasible, full-scale clinical trial of at least one antiepileptogenic intervention.

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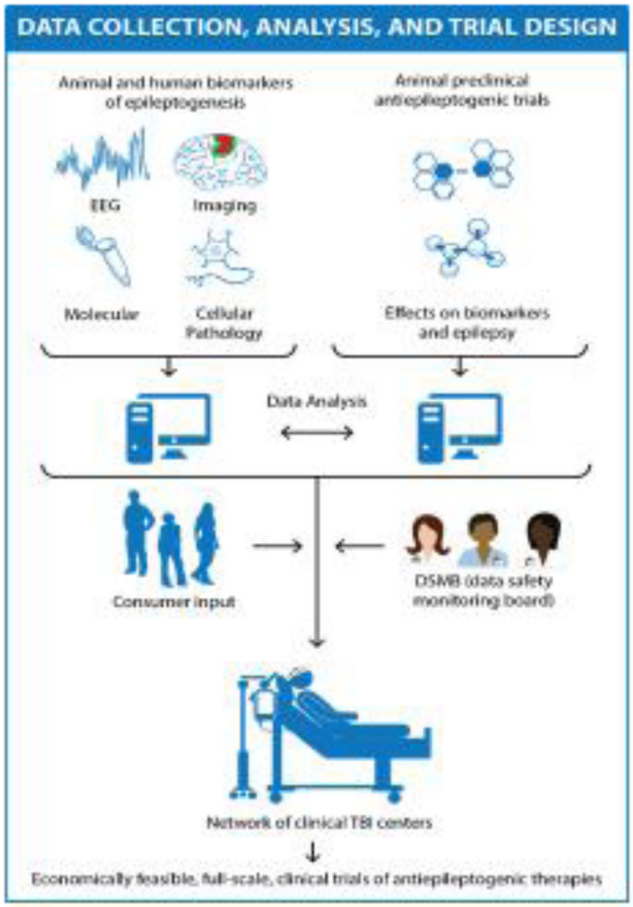

Figure 1.
Data collection, analysis, and trial design

Figure 2.
Organization of EpiBioS4Rx