CENTER ON HUMAN DEVELOPMENT & DISABILITY
UNIVERSITY of WASHINGTON

CHDD Outlook 2019 Issue #5
News from the Center on Human Development and Disability at the University of Washington

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Preventing Epileptogenesis with Investigational New Treatments

by Stacey Aggarwal

Epilepsy is a complex neurological disorder that lacks a unifying etiology but can be broadly described as excessive or irregular activity of neuronal cells in the brain, resulting in seizures. It is estimated that 65 million people worldwide are affected by this disorder. It can develop at any age and can change over time. There are many potential causes of epilepsy including genetics, trauma, brain tumor, cerebrovascular accident or stroke, cerebral infection, and uncontrolled convulsive seizure activity such as status epilepticus. As a result of these numerous variables, each individual case of epilepsy may differ by etiology, mechanism, treatment, and outcome.

There are close to two dozen medications currently available that target various neuronal pathways to help manage seizures in this disorder. However, finding new treatments to prevent epileptogenesis (the development of epilepsy) altogether or modify seizure severity and progression could improve the quality of life for millions of current and at-risk individuals.

H. Steve White, PhD, professor and chair of pharmacy and CHDD research affiliate, is working to identify new therapeutics that can modify the development of this disorder to prevent or change disease progression. “Prevention of epilepsy in the susceptible person is the Holy Grail of epilepsy research. But from a practical perspective, the identification of treatments that could reduce the overall burden of the disease state by decreasing seizure severity, changing the type of seizure, or preventing therapy resistance would be a big win for a lot of patients with epilepsy,” White says. He works on this project to identify new therapeutics with co-investigator Melissa Barker-Haliski, PhD, research assistant professor of pharmacy and CHDD research affiliate.

H. Steve White is actively engaged in the discovery and development of novel therapeutics for the treatment of epilepsy. White leads a broad-based research program aimed at gaining a further understanding of the factors that contribute to the expression and prevention of seizure activity.

“Epilepsy Prevention is the Holy Grail”

A major hurdle in identifying preventative treatments for epilepsy is the identification of risk factors. White elaborates, “One of the challenges clinically will be: How do you identify the patient at risk? Not every patient with a traumatic brain injury will develop epilepsy, only about 25%.” Even in the case of two patients with clinically identical traumatic brain injuries, for example, one may go on to develop epilepsy while the other recovers normally. White hopes that future research will help identify what factors contribute to disease progression. This would help better identify those at risk of developing epilepsy earlier and lead to the identification and development of “disease modifying” treatment options.

White points out further that, “Ethically, it’s difficult to ask a patient with a 1 in 4 chance of developing epilepsy to take a treatment that they may not need and with little known about the impact on their brain repair mechanisms or the rest of their body.” He suggests that in order to design treatment strategies for the prevention of epilepsy, more needs to be known about risk factors that affect an individual’s disease trajectory. The identification of reliable and predictable biomarkers that mark disease progression and treatment outcome is sorely needed to face this hurdle and advance the treatment of epilepsy.

A Clinically-Relevant Model of Epileptogenesis

White’s goal in his current project is to identify compounds that prevent or modify epileptogenesis after an initial insult such as status epilepticus (SE). He points out, “There are no approved drugs that prevent or modify epilepsy, so this is very new territory.” Experimentally, White investigates this question by treating rats with kainic acid, a potent excitotoxin which leads to severe SE.

If left untreated, SE will produce significant neuronal cell damage and, ultimately, epilepsy. Experimental rats treated with kainic acid are monitored using video-EEG. This combined approach allows for continuous observation of the rats while monitoring brain activity over several days to weeks.

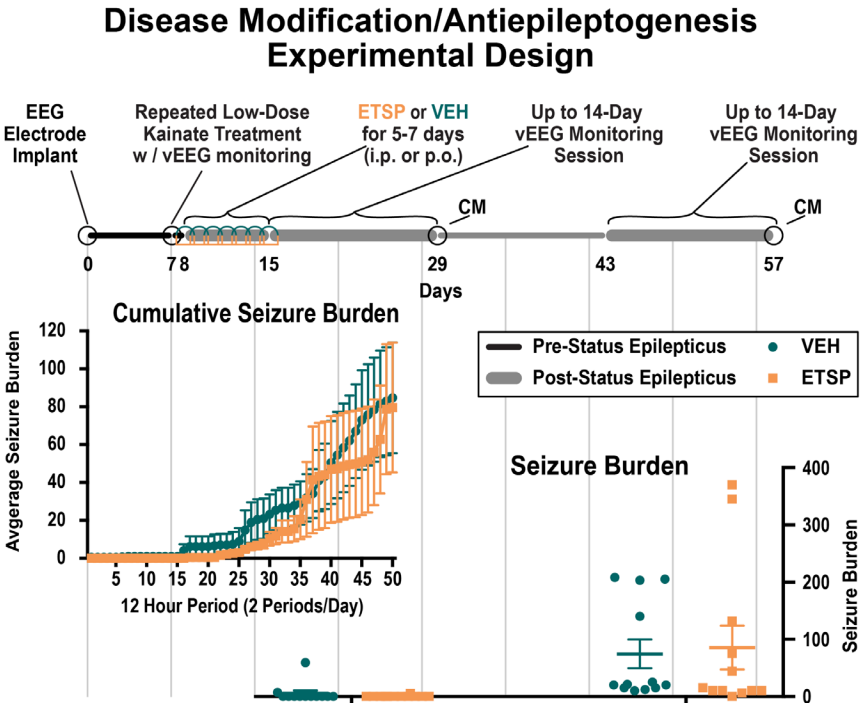
After rats are treated with kainic acid, the White lab reviews the video-EEG data for signs of spontaneous seizure activity and the onset of epilepsy. An initial SE event is considered to be the insult that initiates the epileptogenic process. When both EEG and video confirm a second clinical convulsive seizure event, the rat is diagnosed with epilepsy. White and others have demonstrated that this model closely recapitulates many characteristics observed in human epilepsy following an initial SE event or other neurological insult.

In their efforts to identify potential disease-modifying and disease-preventing therapies, White and his colleagues begin treating rats with an investigational therapy within a few hours after SE onset. Treatment duration depends on a number of factors, such as the predicted mechanism of action and pharmacokinetics of the drug. The EEG and behavior of treated rats is then continuously monitored 24 hours a day, 7 days a week to assess the impact of treatment on epilepsy development and seizure severity.

White points out that, “These studies are conducted very much like a clinical trial, using a rigorous double-blinded, placebo controlled trial design.” This preclinical work is supported by the NINDS Epilepsy Therapy Screening Program, through a sub-award from the University of Utah (Karen S. Wilcox, PI of the Utah Program). This work is one aspect of NINDS efforts to support the discovery of anti-epileptogenic and disease-modifying therapies for epilepsy.

Treatments to Modify Epilepsy Progression

Although prevention is ideal, methods to decrease the burden of epilepsy are also important areas to explore. White points out that about 30% of patients with epilepsy are resistant to currently available anti-seizure treatments. Little is known about the cause of therapy resistance in epilepsy. Additionally, it has been challenging to identify new therapies to control seizures after other available treatments were unsuccessful without impairing normal neuronal processes. The White laboratory is constantly evaluating new model systems for therapy discovery in the hope that someday a transformative therapy will be identified for patients with therapy resistant epilepsy.



White also points out that seizures are not the only clinical manifestation that an individual with epilepsy faces. For example, he points out, “Patients with epilepsy often deal with significant comorbidities that can include anxiety, depression, learning and cognitive issues, all of which can significantly impair a patient’s quality of life.” Unfortunately, complete seizure control does not guarantee the control of comorbidities. Understanding the molecular causes of these comorbidities and how they relate to epilepsy can advance new therapy discovery. The pursuit of therapies that prevent or modify epilepsy-related comorbidities is also an important aspect of the work being conducted by White and his colleagues.

The seizure burden of rats administered VEH (0.5% methylcellulose) or Epilepsy Therapy Screening Program (ETSP) was quantified up to 6 weeks post kainic acid-induced status epilepticus insult by chronic video-EEG monitoring. (CM, comorbidities; SE, status epilepticus)

CHDD is an interdisciplinary center dedicated to the prevention and amelioration of developmental disabilities through research, training, clinical service, and community outreach. CHDD includes the University Center of Excellence in Developmental Disabilities and the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Center.

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