EPILEPSY CURRENTS

Epilepsy Benchmarks
Epilepsy Resources and Updates

2014 Epilepsy Benchmarks Area III: Improve Treatment Options for Controlling Seizures and Epilepsy-Related Conditions Without Side Effects

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The Epilepsy Benchmark goals in Area III focus on making progress in understanding and controlling seizures and related conditions as well as on developing biomarkers and new therapies that will reduce seizures and improve outcomes for individuals with epilepsy. Area III emphasizes a need to better understand the ways in which seizures start, propagate, and terminate and whether those network processes are common or unique in different forms of epilepsy. The application of that knowledge to improved seizure prediction and detection will also play a role in improving patient outcomes. Animal models of treatment-resistant epilepsy that are aligned with etiologies and clinical features of human epilepsies are especially encouraged as necessary tools to understand mechanisms and test potential therapies. Antiseizure therapies that target (either alone or in combination) novel or multiple seizure mechanisms are prioritized in this section of the Benchmarks. Area III goals also highlight validation of biomarkers of treatment response and safety risk, effective self-management, and patient-centered outcome measures as important areas of emphasis for the next five to ten years.

Epilepsy Currents, Vol. 16, No. 3 (May/June) 2016 pp. 192–197

Key Advances in Area III

Developing and Refining Animal Models

Animal models are needed to test interventions targeted to various features of epilepsy, such as delaying the latency between initial insult and onset of spontaneous seizures, preventing the progression of epilepsy severity over time, converting pharmacoresistant to anticonvulsant-responsive seizures, and alleviating behavioral comorbidities. Progress has been made to address some of these aspects of disease modification and to identify etiologically relevant epilepsy animal models. One etiologically relevant animal model of cerebral viral infection is that produced by inoculation of mice with Theiler murine encephalomyelitis virus, which produces a strong neuroinflammatory reaction coupled with seizures and the development of long-term cognitive deficits (1). A similar model of cerebral malaria produces epilepsy that appears dependent on an intact complement pathway (2).

Posttraumatic epilepsy is a leading cause of epilepsy in young adults. Much effort has been devoted to developing etiologic animal models that lend themselves to drug screening and can be used to understand mechanisms of epileptogenesis in this condition. A recent study (3) reported the parametric optimization of a rat fluid percussion model that results in focal, nonconvulsive, brief seizures. In this model young (1 month old) male Sprague Dawley rats are subjected to an abrupt percussive injury to the parietal cortex. Within

a week in this model, most animals develop high-amplitude propagating spike trains in the theta frequency range that last from 1 second to about 5 minutes and are time-linked to stereotyped behaviors. Although similar EEG activity and behaviors are seen in clinically normal older male Sprague Dawley rats (4, 5), such activity is reported to not occur in sham-operated young rats (3, 6). Eastman et al. (3) systematically evaluated the effects of number and placement of EEG electrodes, seizure definition, and group size to determine the minimum recording time needed to detect a 50% change in seizure frequency with 80% statistical power. Surprisingly, with optimum electrode montage 24-hour recordings from six rats are sufficient, a much briefer time and a smaller number of animals than would generally be required to detect a significant effect based on a statistical power analysis. This model was used to demonstrate that transient cooling of the injured cortex (2° for 5.5 weeks) was neuroprotective and prevented the development of seizure-like events (6). Whether the briefer bursts represent actual seizures remains controversial although the careful parametric analysis (3) illuminates the way to more efficient preclinical trials in this and other models.

A zebrafish model of Dravet syndrome (Scn1a homozygous mutant) was recently introduced (7) and used to screen a small library of marketed compounds in an effort to identify new classes of anticonvulsants for this genetic epilepsy (8). Testing a known drug that has proven effective in Dravet syndrome (fenfluramine) indicated activity, providing validation. Another antiseizure drug (dimethadione) was identified in the screen but has not yet been evaluated for clinical activity in Dravet syndrome. A limitation of the model is that concentrations at relevant targets are not know (concentrations of fenfluramine 500 to 2,500-fold, those that are achieved with clinically relevant doses, were used, but access may be limited). Moreover, many drugs safe for humans cause mortality in zebrafish, and it can be difficult to separate antiseizure activity from neurological toxicity. Zebrafish could be produced with patient-specific mutations to screen for agents that might provide a personalized treatment approach for an individual patient.

Identifying Biomarkers

Biomarkers of medical treatment response remain elusive, but novel techniques may improve surgical localization and postsurgical deficit prediction. A pilot study using 7-Tesla MRI glutamate chemical exchange saturation transfer (GluCEST) (9) correctly lateralized the seizure focus in 4 patients with nonlesional temporal lobe epilepsy based on conventional 3-Tesla MRI. The magnetic resonance spectra, available for a subset of 4 patients and 11 control subjects, corroborated the GluCEST findings. Hippocampal volumes were not significantly different between hemispheres. GluCEST allowed high-resolution functional imaging of brain glutamate and has potential to identify the epileptic focus in patients previously deemed nonlesional.

Development of novel functional MRI (fMRI) memory tasks may improve identification of postsurgical memory outcome. Over the past 15 years, many attempts have been made to identify patients at risk for developing verbal memory deficits after a standard anterior temporal lobectomy (anterior temporal neocortex and mesial temporal structures). These efforts have been only partially successful. Recently, asymmetry of fMRI activation related to an in-scanner verbal memory encoding task with post-fMRI recall probe predicted memory outcomes following anterior temporal lobectomy (10). These efforts show promise for improved fMRI signatures that will non-invasively identify patients at risk for postsurgical memory deficits.

High-mobility group box 1 (HMGB1) is a nonhistone chromatin chaperone protein that, upon injury or initiation of an inflammatory reaction, is translocated from the nucleus to the cytoplasm and eventually secreted, finding its way into the bloodstream. Oxidative stress converts cysteines 23 and 25 from the reduced -SH to the oxidized S-S form, which activates the NFκB and other inflammatory pathways (11). HMGB1 has received attention as a potential prognostic biomarker for cancer (12), stroke (13, ClinicalTrials.gov ID NCT01705353), and other conditions involving tissue injury coupled with sterile inflammation. HMGB1 is also translocated to the cytoplasm in astrocytes of mice and people with epilepsy (14), and it appears in the serum of rats 12 hours after status epilepticus, and is also found in the serum of patients with epilepsy (15, 16). HMGB1 thus appears promising as a serum biomarker of inflammation-associated brain injury during the process of epileptogenesis.

Understanding Seizure Dynamics

Recent advances in understanding seizure propagation could improve surgical outcomes for patients. A study of the spatiotemporal dynamics of seizure propagation on intracranial EEG (17) reported better surgical outcomes in patients with a consistent and organized pattern of seizure propagation from seizure to seizure than in patients without consistent spatial organization of activity during recruitment. Seizures can be recorded in humans with high-resolution microelectrodes to distinguish different seizure types at multiple scales (18). Such studies require development of novel analytic tools to process the large amounts of data. In one study, high-bandwidth recordings through microelectrode arrays in presurgical patients revealed a rather compact seizure-generating ictal core surrounded by a larger ictal penumbra that was sometimes recruited into the seizure wavefront (19). An improved understanding of how the seizure-initiating core recruits brain regions that generate large amplitude voltage fluctuations provides novel information that may improve surgical treatment of epilepsy and highlights the slow spread of massive local activity across a large extent of cortex during seizure.

An alternative approach is to quantify the basic dynamics of seizures. Recent work using bifurcation analysis (20) identified several inherent dynamic properties of seizure onset and offset that are conserved across multiple species and brain regions. In particular, within a simple computational model the onset and offset of ictal-like discharges could be described as mathematical events, a saddle-node and homoclinic bifurcation, respectively. These bifurcations require a baseline shift at onset, consistent with the direct-current voltage change seen in wide bandwidth recording and logarithmic scaling of interspike intervals at offset. These predictions were confirmed in humans and zebrafish.

Improved Seizure Detection, Prediction, and Termination

Advances in implantable devices for epilepsy saw several milestones in the past years. The feasibility of seizure predic-

tion was demonstrated in humans in a landmark study by Australian investigators. In this study, a novel implantable device sent intracranial EEG measurements via telemetry to a personal handheld computer capable of real-time analytics. The computer provided seizure forecasts, i.e., estimates of low and high seizure likelihood that were found to be significantly better than chance (21). Further work is ongoing to replicate findings based on non-invasive recording techniques of physiological signals.

An effort to crowd-source solutions to the problems of seizure detection and prediction from intracranial EEG data took the form of a contest sponsored by the National Institutes of Health, American Epilepsy Society, and Epilepsy Foundation of America. The contest was hosted on Kaggle.com and sparked interest from engineers all around the world. In just a few months, teams with no prior expertise in epilepsy were consistently achieving accuracy as high as 84% for classification of interictal versus preictal data clips from humans and canines with focal epilepsy. A total of 504 teams participated in the two contests, one for detecting seizures and the other for predicting seizures using huge intracranial EEG data sets. The Seizure Detection Challenge was won by an Australian software engineer. The Seizure Prediction Challenge was a tight seven-way race, with first place awarded to a team of five engineers and scientists who decided to join forces as the contest progressed. The data and software are freely available to researchers worldwide by the National Institute of Neurological Disorders and Stroke, University of Pennsylvania, and Mayo Clinic (ieeg.org and msel.mayo.edu) (22).

Improve Antiseizure Therapies That Target Novel or Multiple Seizure Mechanisms

Therapeutic advances have been made during the past several years in medication, surgical, and stimulation-based approaches to controlling seizures, some with improved side-effect profiles. However, all therapeutic interventions aimed at controlling seizures have side effects, and novel therapies may present other unforeseen adverse events that limit use and require additional research to address in an iterative manner.

Ezogabine, also known as retigabine, is a Kv7 potassium channel opener that was approved for adjunctive therapy for focal seizures in individuals with refractory seizures who are 18 years and older. Efficacy for this first-in-class agent was demonstrated in phase III clinical trials (23, 24). Safety issues associated with ezogabine include dizziness, somnolence, confusion, and fatigue, which are all common for CNS-acting drugs. However, use of ezogabine is also associated with increased risk of neuropsychiatric events (including confusion, hallucinations, and psychosis), urinary retention, increased post-void residual volume, and blue discoloration of skin and eyes. The retinal and skin abnormalities may be permanent and thus resulted in labeling changes required by the U.S. Food and Drug Administration in 2013 (25). For these reasons, despite the advance represented by its novel mechanism of action, ezogabine has a boxed warning and is generally not considered for use until seizures have failed to respond to several other antiseizure medications (26).

In January 2014, perampanel, a new antiseizure drug acting in part as a noncompetitive AMPA receptor antagonist, was launched in the United States. Efficacy was demonstrated in studies of both focal-onset (27) and primary generalized tonic-clonic (28) seizures although adverse events, including dizziness, somnolence, ataxia, fatigue, and neuropsychiatric events (including aggression and homicidal ideation), were flagged as side effects in some patients (see the Area IV report and [29]). Three phase III studies published in 2015 (30) documented the efficacy of perampanel in patients with drug-resistance partial seizures after the conversion from double-blind placebo to open-label perampanel.

Brivaracetam, the 4-*n*-propyl analog (levetiracetam) was approved by the U.S. Food and Drug Administration in February 2016 as adjunctive therapy for the treatment of partial-onset seizures in patients with epilepsy aged 16 years and older. Brivaracetam was discovered in a medicinal chemistry campaign seeking to enhance the binding affinity to SV2A, the molecular target of levetiracetam, and is one of the few rationally designed antiseizure drugs (31). The most common side effects reported in clinical trials included drowsiness, dizziness, fatigue, nausea, and vomiting (32). The extent to which brivaracetam will provide advantages to levetiracetam remains to be determined.

Several novel invasive approaches have been introduced to patients with epilepsy in the past several years. Deep brain stimulation for epilepsy continues to show promise. Two recent studies have demonstrated the long-term efficacy of therapeutic brain stimulation using either duty cycle stimulation of the anterior nucleus of thalamus (33), or focal stimulation targeted to the seizure focus that is triggered by certain EEG patterns (34). Both therapeutic stimulation approaches showed continued improvement in efficacy with time, demonstrating that brain stimulation is a durable therapy for focal epilepsy. Responsive stimulation has been shown to reduce seizure frequency and improve quality of life in patients with treatment-refractory partial-onset epileptic seizures (34–36). Moreover, at 2 years, there was a small but significant improvement in naming in patients with neocortical seizure onset, as well as improvement in learning in patients with seizure onset from the mesial temporal structures (37). The Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial has shown efficacy in reducing seizure burden in patients with medically intractable epilepsy, and gains were reported in quality of life along with an improvement in several neuropsychological measures (33). The infrequent but most common serious adverse event in the responsive neurostimulation and SANTE trials was infection at the implant site. Pilot studies point to stereotactic laser ablation being efficacious, and it seems to be associated with fewer cognitive consequences than traditional open resection approaches (38), arguing that many of the cognitive deficits associated with resective surgery reflect collateral surgically imposed damage to the tissue adjacent to the ictal focus (See also the Area IV report). While the initial data on quality of life and adverse events of these alternative surgical interventions is encouraging, ongoing systematic and standardized evaluation of large patient cohorts will be important for more definite assessment of their utility in clinical practice.

Improve Self-Management

Epilepsy self-management refers to a number of behaviors and actions that a person with epilepsy can employ to promote seizure control and enhance quality of life. Collection of infor-

mation has also driven by advances in wearable devices and portable healthcare technology as well as phone and device applications. Various programs of self-management have been developed, and recent Cochrane reviews of the available self-management tools and intervention programs through 2013 were evaluated for children and for adults. In both cases, the quality of the evidence in the analysis was considered relatively low. Recommendations for additional research in this area included the use of randomized controlled clinical trials (rather than observational studies), sufficient detail about the intervention, and sufficient numbers of interventionalists (if used) so that individual-specific variables such as level of training or interaction style do not confound results (39, 40). A bright spot in this area is the Centers for Disease Control and Prevention's Managing Epilepsy Well Network, which is advancing the field of self-management research and tools for epilepsy (41). In 2015, results of a randomized controlled trial of a self-management program for adults showed improved Epilepsy Self-Management Scale and quality-of-life scores in the intervention group that persisted for up to 6 months after the intervention (42). Further, investigators working with the Managing Epilepsy Well Network have published an informatics-based approach using an epilepsy ontology to maximize the secondary use of clinical data; this proof of concept could be more broadly applicable to data sharing across many other areas of epilepsy research as well (43).

Looking Forward: Challenges and Opportunities

New therapies that have fewer, or more tolerable, adverse consequences than current treatment approaches are under development in several sectors. For example, preliminary experimental work suggests that focal cooling of perilesional neocortical seizure foci may reduce seizure activity (6, 44). Pilot human studies also suggest that systemic therapeutic hypothermia may represent an effective means toward control of acute seizures or status epilepticus (45, 46). This is a promising novel approach in the management of acute seizures. Seizure detection using noninvasive wearable sensors, smart watches, and markers of multiple physiological signals, including ictal tachycardia, is an area of active clinical research and development. In addition, research to optimize existing antiseizure medications to eliminate problematic side effects is also underway, tentatively using comparative effectiveness and "big data" approaches. In some cases, a better understanding of the fundamental neurobiology that generates neuropsychiatric symptoms such as hallucinations, suicidal ideation, aggression, or hostility will be necessary, as it is possible that the same mechanism of action that suppresses seizures is also involved in generating neuropsychiatric symptoms. Likewise, comorbid pharmacotherapeutic effects on sleep and vigilance may need to be approached more comprehensively. The reciprocal interactions between sleep/circadian abnormalities and seizures need to be elucidated and could suggest opportunities for chronotherapy and individualized epilepsy management strategies to improve quality of life and seizure control. Off-target effects could also contribute to problematic side effects, and these effects could be amenable to optimization through medicinal chemistry. Activities are also underway to increase the overall value of preclinical animal model testing in drug development for epilepsy (47).

New drug targets have been identified that will, if ultimately shown to be effective in clinical trials, expand the repertoire of anticonvulsant mechanisms of action (48). Metabolic control of excitability is an area of growing interest, given the long history of success with the ketogenic diet in children, and more recently with adults, with epilepsy refractory to other medications. Sada et al. (49) demonstrated that inhibition of lactate dehydrogenase (LDH) suppresses seizures in both acute and chronic epilepsy models. The investigators then assessed whether existing antiseizure drugs had LDH-inhibiting properties, and found that stiripentol, a GABAergic agent, is also a potent inhibitor of LDH, suggesting metabolic control as an additional mechanism of action for this drug and further supporting the rationale for new drug development on metabolic targets. Mechanistic/mammalian target of rapamycin (mTOR) pathway inhibitors are also in development as potential antiseizure targets in tuberous sclerosis complex (50), and they may also have potential for controlling seizures associated with focal cortical dysplasia due to brain somatic mutations with a direct mechanistic link to mTOR overactivation (51–53). It remains to be seen whether mTOR-based drugs may be useful in acquired epilepsies as well.

An initial Phase 3 trial of cannabidiol as adjunctive treatment of convulsive seizures in Dravet syndrome achieved a highly significant positive outcome. This is the first step in filling the void of Class I evidence with cannabiadiol for epilepsy. A second pivotal trial of cannabidiol in Dravet syndrome is in progress, as are two Phase 3 trials in Lennox-Gastaut syndrome, and a Phase 3 trial in tuberous sclerosis complex. The basic science underpinning the scientific rationale for using cannabinoids in epilepsy has also been growing in recent years. Although cannabidiol has low affinity for CB1 and CB2 cannabinoid receptors, it may indirectly affect endogenous cannabinoid mechanisms or it could exert its therapeutic activity on non-cannabinoid-related targets. Endogenous are one of the body's mechanisms to regulate excitability through retrograde inhibition of neurotransmitter release, and possibly through other mechanisms as well. Cannabinoids modulate GABAergic interneurons and interneuron-generated network rhythms (54). Understanding the principles that govern the control and plasticity of the endocannabinoid system in response to recurring spontaneous seizures will likely be critical to understanding the potential and limits of cannabinoid-based therapies for various forms of epilepsy.

Modulation of homeostatic processes is an alternative strategy for suppressing seizure-promoting events. Adenosine acts as an endogenous antiseizure agent (reviewed by [55]), and recent work demonstrating a rise in adenosine levels just prior to seizure termination in animal models and human epilepsy patients (56) further supports the adenosine system as an important homeostatic target for new antiseizure drug development. Adenosine may have a role as an anti-epileptogenic agent as well (See the Area II report).

Finally, Area III goals also highlight validation of biomarkers of treatment response and safety risk as well as patient-centered outcome measures as important areas of emphasis for the next five to ten years. Although less progress has been apparent in these areas to date, they remain, nonetheless, important areas in which advances can help to reduce the burdens of epilepsy on individuals and families.

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