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Introduction to the ‘Jasper’s Basic Mechanisms of the Epilepsies’ workshops

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Summary

In 1969, H.H. Jasper, A.A. Ward, and A. Pope and the Public Health Service Advisory Committee on the Epilepsies of the National Institute of Health published the first volume on Basic Mechanisms of the Epilepsies (BME). Since then, basic and clinical researchers in epilepsy have gathered together each decade to assess where epilepsy research has been, what it has accomplished, and where it should go. In 1999, the third volume of BME was named in honor of H.H. Jasper. Projected for 2011, the fourth edition of Jasper’s BME will (1) synthesize the role of interactions between neurons, synapses, and glia in the initiation, spread and arrest of seizures, (2) examine the molecular, cellular, and network plasticity mechanisms that subserve excitability, seizure susceptibility, and ultimately epileptogenesis, (3) provide a framework for expanding the genome of rare mendelian epilepsies and understanding the complex heredity responsible for common epilepsies, (4) explore cellular mechanisms of the two main groups of presently known Mendelian epilepsy genes, namely ion channelopathies and developmental epilepsy genes, and (5) for the first time, describe the current efforts to translate the discoveries in epilepsy disease mechanisms into molecular and cellular therapeutic strategies in order to repair and cure the epilepsies. For an expanded treatment of this topic see *Jasper’s Basic Mechanisms of the Epilepsies, Fourth Edition* (Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, eds) published by Oxford University Press. Available on NCBI Bookshelf.

Keywords

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In February, 2010, the International League Against Epilepsy (ILAE) Commission on Classification and Terminology revised the classification of seizures and the many forms of epilepsy. Epilepsies are now classified into three types; genetic, structural/metabolic, and unknown (Berg et al, 2010). This new classification, conceived with an emphasis on basic mechanisms, represents important changes in concept and approach – changes which Jasper’s BME had espoused in its 1999 classification of epilepsies as necessary for solving the essential questions of how seizures start and stop, and for aligning the underlying causes of epilepsy phenotypes with their molecular and cellular disease pathways (Delgado-Escueta et al, 1999). The current 2010 Epilepsia supplement on Jasper’s Basic Mechanisms of the Epilepsies which presents an overview of contributions that will appear in the 2011 Jasper’s BME book, continues in this strategic direction. Four major areas have been organized to address a multidisciplinary range of issues: the fundamentals of neuronal network excitability that produce seizures and epilepsy; how seizure mechanisms contribute to epileptogenesis; genetic mechanisms of heritable susceptibility to epilepsy in the developing brain; and new mechanisms in epilepsy therapies. As in previous efforts, the participants in the 2009 Jasper’s BME Workshops (Fig. 1), held in Yosemite, looked toward the next decade and prioritized research areas where efforts should be accelerated and enhanced (see Table 1).

Fundamentals of neuronal excitability relevant to seizures and epilepsy

Neurobiological research has progressed swiftly during the last decade, providing detailed information on the molecular, pharmacological, and functional characteristics of voltage- and ligand-gated membrane signaling mechanisms regulating neuronal network excitability. Along with the views originally formulated by Herbert Jasper and his former student Peter Gloor, thalamocortical and reticulothalamic mechanisms have been firmly established as the substrate for genetic generalized seizures. An eminent example is the absence seizure phenotype which is dependent on thalamocortical circuitry for expression, and where details of cellular and molecular events are defined. Burst firing in thalamocortical circuitry of GABAergic reticular thalamus neurons is activated by low-voltage activated T-type calcium channels producing EEG spike-wave discharges and absence seizures. GABA release from reticular neurons hyperpolarizes thalamocortical neurons supported by an increased tonic GABA-A current. GABA-B receptors in turn modulate this tonic current, explaining the anti-absence action of GABA-B antagonists. Myoclonic and tonic-clonic convulsive seizures may also be circuitry dependent although their specific cellular and molecular networks are not as well defined.

Analysis of the mechanisms of high-frequency oscillations has furthered our understanding of how perturbations in fundamental neuronal activity patterns – overlapping those involved in learning and memory – become relevant in the generation of partial epileptic discharges as well as in epileptogenesis. Imaging and computer-based modeling of neuronal networks underlying epileptic discharges is also providing us new and valuable information and are helping us to understand neuronal network synchronization under physiological and pathological conditions. As these basic advances continue, new properties of abnormal signaling in brain networks, such as pathologic high frequency oscillations (200–600 Hz) may provide informative prognostic markers, and point to pathogenic mechanisms that link

models to human epilepsies, allowing the development and translation of new therapeutic tools and anti-epileptogenesis drugs.

Mechanisms of seizure susceptibility and epileptogenesis

Major strides have been made in the last decade to describe how brain damage leads to the chronic and enduring condition of spontaneous seizures, a process defined as epileptogenesis. Accumulating evidence show several events occur as epileptogenesis is acquired in the temporal lobe: 1) the progressive formation of new recurrent excitatory circuits such as mossy fiber sprouting; 2) the selective and progressive loss of specific, vulnerable, GABAergic interneurons, while glutamatergic activity increases; 3) neuronal loss and dentate granule cell dispersion, and 4) enhanced neurogenesis of dentate granule cells, and granule cells with with abnormal hilar basal dendrites. Mossy fiber sprouting of excitatory axons and establishment of new synaptic connectivity is accepted as a ubiquitous epileptogenic response to neocortical or hippocampal damage. Granule cells with basal dendrites, suspected of being newborn neurons, are highly interconnected with each other and with adult granule cells, and may act as hubs for excitatory activity and enhance hyperexcitability in the dentate network. Axonal sprouting is now accepted as a common neuropathological feature in acquired temporal lobe epilepsy produced by trauma, hypoxia/ischemia, stroke, febrile seizures, status epilepticus, and infections. The underlying details, including the time course of granule cell hyperexcitability and spontaneous epileptiform discharges following epileptogenic injuries, the molecular mechanisms preceding and leading to axonal sprouting, and the construction of epileptogenic circuits within the reorganized networks are the focus of this section.

Excitotoxic, necrotic, and programmed (apoptotic) cell death are being analyzed in brain tissue from identified human focal epilepsy cases. The molecular, structural, and physiological plasticity of neural circuits in both human epilepsy and experimental models also remain under intense scrutiny. Within this area, the roles of neurogenesis and neurotrophin biology continue to provide essential information on the mechanisms underlying reorganization and synaptogenesis. These mechanisms (e.g., increases of BDNF expression and enhanced activation of TrkB in the mossy fiber pathway of hippocampus contribute to hyperexcitability, while newly integrated adult-born dentate granule cells may restore inhibition) may illuminate novel targets for the repair of hyperexcitable neural circuits, a relatively new strategic goal in epilepsy therapy. Another longstanding focus of interest is the field of GABA plasticity, with differing approaches in several laboratories describing new insights into the roles of pre- and postsynaptic GABA-mediated transmission and chloride homeostasis. In temporal lobe epilepsy models, expression of the δ subunit is substantially decreased in principal cells but increased in interneurons, and a change in the localization of the $\gamma 2$ subunit from primarily synaptic to perisynaptic sites suggests a subunit switch. In alcohol kindled seizures, remodeling of GABARs also occur, in which EtOH-sensitive extrasynaptic $\alpha 4/\delta$ -containing GABAR-mediated tonic currents in hippocampal and other cells are down-regulated, BZ-sensitive synaptic $\alpha 1/\gamma 2$ -mediated synaptic currents are down-regulated, and compensatory $\alpha 4/\gamma 2$ extrasynaptic and synaptic GABARs are elevated in parallel with increased synaptic sensitivity to alcohol. Finally, the biology of glia-neuron interactions continues to inform the field. Reactive astrocytosis leads to reduced

adenosine- and GABA-dependent inhibition; astrocytes also regulate surface expression of neuronal NMDA receptors and release of glutamate and D-serine; astrocytes produce neurosteroids that reinforce γ -aminobutyric acid receptor A (GABA_A) functions. These cells are also involved in the pathophysiology of brain inflammation by releasing cytokines that produce toxic autocrine or paracrine mechanisms and alter glutamate and GABA receptors function. Glial pathobiology is assuming an increasingly central position in current models of epilepsy, and provides novel therapeutic targets for antiepileptogenesis.

Epilepsy genes and brain development

As widely predicted, the creation of physical and genetic maps of the human genome, announced in 2000, launched the “postgenomic era” for human genetic disease research, and the past decade has witnessed an explosive increase in the number of single genes linked to epilepsy phenotypes. In humans, over twenty syndromes previously considered idiopathic (now called genetic generalized epilepsies in the 2010 ILAE classification) have been shown to arise from mutations in identified genes, and additional loci continue to be mapped from clinical pedigrees. In the laboratory, such genotype-phenotype relationships are emerging at an even faster pace by a reverse strategy, namely, mutating genes in engineered mouse models and screening for epileptic phenotypes. Together, these approaches have unlocked a collection of genes from a broad array of functional biological pathways that exert a major control over brain excitability and synchronization (Noebels, 2003). As examples, mice with P/Q calcium channel subunit gene mutations in *Cacna1a* (*tottering*) and its regulatory subunits, *Cacnb4* (*lethargic*) and *Cacna2d2* (*ducky*) show downstream elevations in thalamic T-type currents, enhancing rhythmicity in thalamocortical networks subserving spike-wave oscillations and producing absence seizures; human mutations in Na_v1.1 channels reduce Na⁺ currents and decrease electrical excitability in GABAergic interneurons and inhibition, contributing to downstream epilepsy, ataxia and the cognitive decline of Dravet’s severe myoclonic epilepsy of infancy. In mouse models of tuberous sclerosis and cortical dysplasia, hyperactivation of the mTOR pathway promotes epileptogenesis and neuropathological abnormalities, and the mTOR inhibitor, rapamycin, prevents or reverses epilepsy and associated phenotypes. For many other genes, much remains to be learned in the laboratory about how both the gain and loss of function leads to epilepsy in the developing brain and how they affect neuronal migration, proliferation, differentiation, genesis and maintenance of synapses and dendrites. Three leading examples of developmental genes causing lissencephaly, epilepsy and mental retardation in infants and young children are *LIS1*, *DCX* and *TUBA1A* that encode microtubule-related proteins involved in neuronal migration and synaptogenesis. Further exploration of these functional pathways will no doubt lead to the identification of additional candidate genes, as well as novel targets for the development of antiepileptogenesis drugs. As the revolution in genomic technology continues, the analysis of complex heredity becomes more tractable, and the next decade will see increased exploration of genetic risk variants that contribute to common sporadic epilepsies, and the extent to which they can modify epileptic phenotypes. The analysis of epilepsy comorbidities will become an important aspect of this search, since their association may point to new common gene pathways and converging mechanisms.

Epilepsy therapeutics

The accelerating pace of discovery in basic epilepsy research is beginning to deliver the molecular pathways and cellular mechanisms that can be targeted in the development of novel therapies. Therefore, for the first time, the editors devote a major section of Jasper's BME to the treatment of epilepsy with an emphasis on its scientific underpinnings.

Since the work of Merrit and Putnam in the 1940's, the discovery of antiepileptic drugs has been based on screening candidate drugs in predictive animal models without regard to mechanisms of drug action. Drugs often reach the market with little understanding of their pharmacodynamic effects. Once they are well established in clinical practice, information eventually emerges on the molecular targets through which they act to protect against seizures (Rogawski and Löscher, 2004). In contrast, over the past decade, several entirely novel antiepileptic drug targets, notably $\alpha_2\delta$, SV2A and KCNQ potassium channels, have been identified in studies of the newer drugs levetiracetam, gabapentin, pregabalin and ezogabine (formerly, retigabine). The efficacy of these drugs enables expanded discovery programs directed at other members within these molecular families as well as screening of chemical libraries for active compounds. This target-based drug discovery effort represents a new paradigm in antiepileptic drug discovery.

Even with the availability of a steady stream of new antiepileptic drugs, some of which act on unique molecular targets, many patients still do not achieve adequate seizure control. This has led investigators to look beyond drugs to nontraditional treatment approaches (Rogawski & Holmes, 2009). Dramatic progress has been made in at least one older nonconventional treatment approach, deep brain stimulation, which is likely to soon become available as a clinical treatment option. Other older nontraditional approaches that continue to be investigated include hormonal and dietary strategies. At the same time, emerging gene and cell-based treatment strategies are being applied in epilepsy. Promising results have been obtained in animal models and by the fifth edition of Jasper's BME, we hope to have a better sense of the practical feasibility of these approaches.

While researchers are opening new frontiers in biological therapies, there has been an interest in understanding the neurobiological bases of pharmacoresistance, which has led to new ideas on how to overcome drug refractoriness, some of which are already being tested in the clinic.

Closing summary

Finally, in line with the view that understanding epileptogenesis is a critical research priority (Table 1), investigators are seeking antiepileptogenic treatment strategies with the ambitious objective of preventing the onset of epilepsy or reversing it once it has become established. New animal models based on mutations of human genetic generalized epilepsies designed to investigate antiepileptogenesis, disease modifications and cures are under development. Successful approaches will likely have little similarity to drugs that are currently used to protect against seizures. Recognizing that symptomatic treatments for neurological disorders have been easier to come by than those that correct an underlying brain defect, there is

nevertheless optimism that these new approaches will eventually lead to the repair, cure and eradication of some forms of epilepsy.

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Figure 1.
Participants in the Jasper's Basic Mechanisms of the Epilepsies Workshops, Yosemite National Park, California, 2009

Table 1

Top Priority Research Areas: Where should epilepsy research go in the next 10 years?

1. Anti-epileptogenesis: What to target? Causality? When?
<p>A. Monitoring: high throughput for animal models and people, anticonvulsant efficacy, seizure detection/prediction</p> <p>B. Triggered mechanisms: stress, sleep, fever, hormones</p>
2. Determine genomes for epilepsies, genetic risks, prediction
<p>A. Understanding how mutations produce human epilepsy phenotypes</p> <p>B. Exploring the common background shared by genetic epilepsy</p> <p>C. Translating and validating relevant experimental models to corresponding human epilepsies</p>
3. New therapies: stem cells, interneuronal grafts, gene replacement therapy, drugs targeted to disease mechanisms or etiology
4. Pharmacoresistance, new (targeted) drug development, drug delivery
5. Plasticity in regulatory/signaling pathways during epileptogenesis
6. Synaptic plasticity and abnormal network synchronization
7. Drug withdrawal kindling and seizure susceptibility
8. Role of glia in epilepsy and in GLU/GABA regulation

* Jasper's BME authors ranked research areas and their rankings are reflected in the order in the table above