Models for Epilepsy and Epileptogenesis: Report from the NIH Workshop, Bethesda, Maryland

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Summary: Purpose: The workshop explored the current problems, needs, and potential usefulness of existing methods of discovery of new therapies to treat epilepsy patients. Resistance to medical therapy (pharmacoresistance) and the development of epilepsy (epileptogenesis) are recognized as two of the major problems in epilepsy treatment today. At the same time, there is growing awareness that the development of new therapies has slowed, a trend that has economic and scientific roots. To move toward new and more effective therapies, novel approaches to therapy discovery are needed.

Methods: A workshop was held in March 2001 with the charge to develop a plan to move the exploration and discovery process forward. Participants from academia, government, and industry reviewed the current status of epilepsy therapy and explored the identification of potential new therapies.

Results: At the end of the 2-day meeting, the panel made a series of recommendations. The two major recommendations were (a) to establish a means for continuing the examination of new approaches to therapy discovery, and (b) to identify models and approaches to therapy discovery that may identify treatments that are more successful than those available. Further recommendations were made to support the development of technology (miniaturization, computerization, video monitoring, etc.) to facilitate the use of the new models and to identify the mechanisms of therapy success and failure.

Conclusions: Understanding the epidemiology of therapy resistance and providing support for new approaches to therapy development were identified as key issues for introduction of new and more effective treatments. Key Words: Epilepsy—Models—Antiepileptogenesis—Resistant epilepsy—Pediatric epilepsy.

Epilepsy is a group of heterogeneous syndromes affecting >50 million people worldwide. Although many new antiepileptic drugs (AEDs) have been introduced in the last decade, ~30% of patients remain pharmacoresistant (1) and have not benefited significantly from the introduction of several new AEDs since 1993. Furthermore, none of the currently marketed AEDs has been shown to prevent the development of epilepsy in susceptible individuals after a variety of central nervous system (CNS) insults including infection, trauma, or febrile seizures (2–5). The poor success in identifying novel therapies that may prevent the development of epilepsy and pharmacoresistance has been partially the result of a lack of experimental models that closely approximate chronic human epilepsy syndromes as well as our poor understanding of the pathophysiologic bases for pharmacoresistance and epileptogenesis.

The need for treatments to prevent epilepsy and to overcome pharmacoresistance was among the driving forces behind the White House–initiated “Curing Epilepsy: Focus on the Future (“Cure”) Conference (March 2000), which charted research directions for prevention of epilepsy in people at risk and for effective and safe treatment for people with epilepsy. One of the goals of the Cure Conference was to develop a series of benchmarks to address the unmet needs of research in an effort to move toward the discovery of an eventual cure. One of these benchmarks was the development, validation, and application of new models for epilepsy as biologic test systems for the development of novel therapies (6).
As the first step in developing better models for drug discovery, the workshop Models for Epilepsy and Epileptogenesis was held March 1–2, 2001. Its specific objective was to recommend ways to stimulate development of new therapies (pharmacologic and nonpharmacologic) for (a) the prevention of adult and childhood epileptogenesis, and (b) the control of adult and childhood pharmacoresistant epilepsy. A group of experts from government, academia, and the pharmaceutical industry, with specialties in animal models, brain imaging, pharmacoresistance, genetics, and pediatric and adult epilepsy syndromes met with representatives from patient advocacy groups and the Food and Drug Administration (FDA) to discuss the current limitations of existing model systems and to recommend a process that will ultimately lead to the identification of novel therapies (see appendix for participant list).

In the discussion that follows, it should be understood that numerous models for seizures, epilepsy, and epileptogenesis involve many animal species and etiologies (7,8). All of these models possess valid scientific rationales to answer specific questions. However, not all may be appropriate for the identification of new therapies for pharmacoresistant epilepsy or for the prevention of epileptogenesis. The purpose of this conference was not to pass judgment on the scientific suitability of an individual model, but rather to initiate discussions concerning which of the myriad test systems might be appropriately applied to the process of identifying new pharmacologic and nonpharmacologic treatments in a way that has more immediate implications for the clinical condition. A few of the important characteristics of a desirable model are reproducibility, cost, and suitability for high-throughput screening of large numbers of drugs. In this discussion, the term high-throughput screening is defined as the means by which possibly hundreds of novel compounds can be tested in a single or a series of standardized assays chosen for the purpose of identifying a particular mechanism of action or for predicting success in the treatment of a particular disease. This process has become another critical tool in the identification of new treatments. It may not be possible to achieve all of these goals immediately, but the primary goal of identifying potentially useful human therapy as opposed to understanding the mechanisms of seizures and epilepsy should be kept in mind when reviewing the discussion that follows.

LIMITATIONS OF EXISTING STRATEGIES IN ANTIPELLEPTIC DRUG DEVELOPMENT

Ultimately, the drug-discovery process uses animal models to ascertain whether a given molecule is biologically active. For more than three decades, laboratory testing of most investigational AEDs has used the maximal electroshock (MES) and the pentylenetetrazol (scMetrazol) seizure models. Dr. Harvey Kupferberg, former director of the Anticonvulsant Drug Development (ADD) Program at National Institute of Neurologic Disorders and Stroke (NINDS), discussed both the successes and the limitations of this highly successful, continually evolving AED-development program. This government-funded drug-discovery program was initiated in an effort to stimulate basic research and to provide an incentive to various research groups for AED development. Since 1975, this effort has resulted in the evaluation of >23,000 compounds for both efficacy and toxicity in a number of different seizure models (9).

This NINDS-sponsored AED-development program has provided a major impetus for the development of several of the older as well as the newly marketed AEDs. Ironically, the successful introduction of the nine new therapeutic agents into the marketplace has had a negative impact on AED development in recent years. There is a sense in industry that the AED market is essentially saturated, so that further investment in this area is not a high priority. This perception has led to a decrease in the development of new epilepsy therapy when advances in our understanding of the pathophysiology of epilepsy at the molecular and genetic level is increasing the chances of finding successful treatments and an eventual cure.

Selection of the models used in the initial screening protocol of the ADD Program was based in part on cost, model efficiency, and the apparent prediction for clinical success by models available at the time. The models also were chosen to encourage the screening of large numbers of compounds from many sources, including industry and academia, so that a wide range of compounds from even very small organizations could be examined for AED potential. These early models (e.g., MES and scMetrazol), although now only a part of the program’s screening process, are still extensively used as the gatekeepers for the identification of promising drug candidates. The question has always been whether the MES and scMetrazol seizure models would identify all potential AEDs or whether these old models would fail to identify compounds that had great potential efficacy but worked through mechanisms not tested by these models. Indeed, despite the introduction into clinical practice of a number of new AEDs since 1993, there has been little reduction in the overall percentage of therapy-resistant patients. The value of relying heavily on these tests is also called into question by the observation that the successfully marketed drug, levetiracetam (introduced in 1999) was ineffective in these models. This observation alone mandates that the research community reevaluate the models currently used in the search for novel AEDs. To this end, one of the central limitations of the “moderately high throughput” (averaging 1,000 compounds/year) MES and scMetrazol seizure models used by most
screening programs is that efficacy is defined by the ability of an investigational drug to limit an evoked seizure in a normal animal (usually mouse or rat). In contrast, clinical seizures associated with human epilepsy evolve spontaneously from an altered CNS substrate.

Awareness of the limitations of acute epilepsy models comes at a critical crossroad. Clearly, the epilepsy research community is undergoing a conceptual shift that is moving away from using models that identify therapies for the symptomatic treatment of epilepsy to those that may be useful for identifying therapies that are more effective in the refractory population and that may ultimately lead to an effective cure in susceptible individuals. To realize the goal of a cure, the molecular mechanisms of the next generation of therapies must necessarily evolve to include targets that contribute to epileptogenesis and pharmacoresistance in relevant epilepsy models.

EPILEPTOGENESIS AND MODELS

The term epileptogenesis applies to a variety of progressive biochemical, anatomic, and physiologic changes that lead to spontaneous recurrent seizures. Many of these changes may occur well before the first onset of clinical seizures. Numerous possible mechanisms underlying this process have been suggested, but no consensus has emerged about which of the observed changes is causal or consequential, how they interact, and how the mechanisms of epileptogenesis may differ with age, from immature to the mature and finally to the elderly brain (6).

A number of models have been suggested as appropriate for the study of mechanisms underlying epileptogenesis, but at the moment there is no general agreement about which models may be most appropriate and relevant to the human condition. More important, none of the available models has been clinically validated. The key feature in any model of epileptogenesis is an interval between the appearance of the epileptogenic abnormality (whether congenital or induced) and the occurrence of the clinical seizures. Numerous animal models of epileptogenesis have been identified and used in research studies designed to increase our understanding of the genetic and molecular abnormalities underlying the development of secondary neuronal hyperexcitability and spontaneous seizures. The study of epileptogenesis would benefit from surrogate markers that are predictive of neuronal/system changes that can be causally associated with the development of chronic epilepsy. Appropriate markers might be anticipated to reflect the structural or functional modifications associated with epileptogenesis and chronic epilepsy (e.g., enhanced excitatory responses, reduced inhibitory responses, and shifts in the subunit composition of receptors and/or channels). However, it is important to note that any putative marker may be reflective of epiphenomena that do not contribute to epileptogenesis. We must be cautious in interpreting any change as possibly causative. Once functionally valid markers are identified, therapies can be designed to inhibit their appearance in a highly specific manner. It also must be remembered that epileptogenesis can have multiple stages so that an effective therapy that is appropriate for one stage may not be appropriate for another. Additionally, it is very likely that therapy that can interfere with the process of epileptogenesis may have a negative impact on the process of normal development or recovery from injury.

Pharmacoresistance and Models

Pharmacoresistance is generally defined as having inadequate seizure control despite accurate diagnosis and carefully monitored pharmacologic treatment (1). For patients with pharmacoresistant epilepsy, seizures may be responsive but not completely suppressed (i.e., frequency decreased but seizures not completely stopped, or frequency unchanged but generalization of seizures prevented). Furthermore, therapy resistance may appear after periods of complete seizure control, an observation that clouds the issue whether pharmacoresistance is a consequence of treatment or is reflective of the progressive nature of a particular epilepsy syndrome. It is unclear whether an individual’s pharmacoresistance is confined to a single compound or to multiple compounds, although clinical experience suggests that multidrug resistance is the most common. The phenomenon of multiple drug resistance also has been observed in cancer therapy and in antibacterial treatment; these fields may provide us with ideas as to how to approach this difficult problem. The mechanisms behind clinical drug resistance are not known but may include receptor or channel insensitivity to the drug, failure of the drug to reach the key regions in the brain, development of tolerance to action of the drug, or the presence of drug-resistant proteins. In this respect, it has been assumed that drugs that enter the CNS are distributed evenly; however, there is emerging evidence to suggest the presence of significant regional variation. There is evidence that multidrug-resistant proteins, which were first described in treatment-resistant cancer, are present in the brains of some patients with drug-resistant epilepsy. More recent work has shown an association of these proteins with models of drug-resistant epilepsy and that the absence of this protein enhances sensitivity to drug therapy.

Several in vivo and in vitro models have been proposed as models of pharmacoresistance on the basis that the seizures do not completely respond to current AEDs. However, the available models have yet to be clinically validated. Ideally, any model should be simple and ame-
nable to high throughput. In vitro systems, however, may not be useful for identifying treatments that avoid pharmacoresistance that results from failure of the drug to reach its targets, as these in vitro systems may not be able to identify whether there will be maldistribution of the drug in the CNS.

**Model Validation**

A critical issue for new therapy identification is the appropriate validation of the model system used. Ideally, a validated model is both sensitive and specific in predicting the clinical success of any new therapy. Model validation is complex and is dependent on the identification of a clinically effective therapy for therapy-resistant epilepsy or epileptogenesis. For a model to be considered valid, it should be highly predictive of clinical response, a requirement that is further complicated by the many forms of epilepsy that have different pathophysiology. It is not clear how any new model for therapy resistance and epileptogenesis should be validated, but it is clear that the current models are not fully adequate. Complete validation is lacking for most, if not all, of the models of epileptogenesis and pharmacoresistance. Until a model becomes clinically validated, evaluations of a new therapy will require testing in several of the proposed models of pharmacoresistance and epileptogenesis. Because it is highly likely that no one model system will be useful for all of the epilepsies, such a multidimensional approach may lead to the identification of molecules/therapies that will display differential profiles. For this reason, it may be most appropriate to start with those models that most closely parallel the human condition. Ultimately, it may be possible to work back and develop high-throughput methods that display a similar pharmacologic sensitivity and specificity.

**PEDIATRIC EPILEPSIES AND DRUG DEVELOPMENT**

Most existing programs for AED discovery have been aimed at identifying new therapies for the adult rather than the pediatric population. Furthermore, many of the marketed AEDs do not have stated indications for children, nor is there information on their pharmacokinetics and safety in children. Even though most childhood epilepsies are responsive to the treatments first developed for adults, there is very high prevalence of pharmacoresistance among children with certain childhood-specific syndromes such as Lennox–Gastaut and infantile spasms. For example, ~90% of children with Lennox–Gastaut are pharmacoresistant to existing therapies.

The pediatric epilepsies are unique in several respects. First, it is not known how the developing brain is affected by those processes underlying epileptogenesis and how the epileptogenic process is modified by the developing brain. Without this information, it will be difficult to design a novel therapy by using a mechanistic approach. Furthermore, it is not known to what extent a particular therapy, if introduced during a critical period, will affect the developing brain. These factors, when coupled with emerging human epidemiologic and animal findings demonstrating age-specific epileptic features, underscore the importance of developing model systems specific for children. Because the mechanisms of epileptogenesis and therapy resistance are likely to be different in developing children, age-specific model systems also are needed. Perhaps the first issue that should be addressed is to define the point in development at which age-specific issues become less important for therapy identification. This issue is complicated by the fact that there are few, if any models for pediatric epilepsy syndromes that parallel the stages of brain development with a time course that allow appropriate comparisons. Development of such models is essential for this area to move forward.

**RECOMMENDATIONS**

After the first day of the workshop, during which these issues were discussed, small groups were assembled to identify potential solutions that will allow the discovery of pharmacologic and nonpharmacologic treatments for pharmacoresistant epilepsy and for the prevention of epileptogenesis to move forward. Although a number of areas were identified by the individual groups, the following list was common across the groups and represents the conference recommendations.

1. **Dissemination of information:** Providing access to the results of the screening process is essential. This point is especially important for existing compounds with identified mechanisms of action that may be tested at some stage in the discovery process. There must be a means for disseminating the results of the studies to the scientific and clinical community in a way that maintains confidentiality for proprietary compounds that are under consideration for development clinically.

2. **Models:** There is an overwhelming need to develop new models and to integrate existing models into the process of therapy discovery for epileptogenesis and pharmacoresistance. A critical step in this process is the thorough evaluation of the proposed models so that compounds that are identified have a high probability of increased clinical success. Similarly, compounds that fail in the models should have very low probability for clinical benefit. This process of model identification should not be construed as a method for passing judgment on the suitability of any model for epilepsy research, because better models for therapy discovery may be
different from those models suited to study the basic mechanisms of seizures and epilepsy. Furthermore, as mentioned earlier, lack of efficacy in one model does not necessarily indicate lack of efficacy in all models. Models that are age appropriate (for the developing, mature, and elderly brain) must be developed, especially for pediatric epilepsy. Possible deleterious effects of pharmacotherapy on the developing brain must be considered. Some attention also should be given to the development of models that may identify gender-specific approaches to therapy. Identification of genetic models with close parallels to human conditions is necessary.

3. Technology development: Models of chronic epilepsy with spontaneous seizures may be the best suited for therapy discovery. Although such models likely represent the closest parallel to the human condition, their use for therapy discovery creates problems with therapy administration and with the documentation of seizures. New technologies for long-term seizure monitoring and drug delivery are essential. In addition, training in the use of this technology must be made available to the larger research community.

4. Mechanistic approach: Although there are many putative mechanisms of action for therapies in current use, little is known about how the available AEDs actually modify seizure activity in an intact system. To give guidance for future therapy development, the utility of specific mechanisms of actions (e.g., sodium channel blockade, receptor agonist or antagonist) in blocking seizures or preventing epileptogenesis must be studied in multiple model systems. In developing this mechanistic approach, it must be realized that the failure of a particular compound with a defined mechanism of action may not be related to the mechanism of action; rather, it may be due to a failure of the compound to reach the appropriate site in the CNS. Design of future studies must take this issue into consideration. Genetic models may play a role in identifying potential mechanisms for therapy development.

5. Surrogate markers: To simplify the process of therapy discovery, a limited number of markers for epileptogenesis and drug resistance must be identified. These markers can then become the focus of study in simplified systems. In the case of epileptogenesis, it is necessary that the identified markers be critical to the process (i.e., not be epiphenomena) and be suitable for simplified, high-throughput screening. The prevention/attenuation of an epiphenomenon, although not ideal, may help in identifying new therapies for drug-resistant epilepsy, particularly if the epiphenomenon is associated with a clinical seizure.

6. Epidemiology: There is little information concerning the natural history of epileptogenesis and drug resistance. An important issue is whether pharmacoresistance is an inevitable consequence of the condition or whether it evolves and could be prevented with an appropriate therapy. To help design appropriate clinical and animal trials, more epidemiologic studies are needed, including the identification of risk factors for the development of epilepsy and drug resistance.

7. Long-term support: The nature of screening for effective pharmacologic and nonpharmacologic therapies is often slow and repetitious and is associated with many failures. Research proposals in this area are less likely to be successful in the traditional peer-review process, which emphasizes productivity and mechanistic research. For this reason, it is necessary to establish a support mechanism that will allow the development of an infrastructure with the essential expertise needed to carry out the studies involved in therapy discovery.

8. Center development: To maintain standards for particular approaches, it is necessary to support existing centers and to develop new ones capable of carrying out large-scale evaluation of compounds by using standardized protocols for mechanistic evaluations of seizure control, drug resistance, and epileptogenesis. A consortium approach may be appropriate for the multifaceted and complex studies that are necessary. Although these recommendations were made across all groups, there also was a consensus that these points were guided by an evolving understanding of the underlying mechanisms of epilepsy, epileptogenesis, and drug resistance. These approaches will no doubt change as our understanding of the pathophysiology of the epilepsies at the molecular and genetic levels evolves.

9. Future role: This conference represented only the beginning of what should be an ongoing process to identify and evaluate models that can be used in novel therapy discovery. Given the breadth of the problem and the approaches that could be taken, a group should be assembled to develop concrete recommendations for additions to the current screening process. This group should be charged with integrating clinical observations with basic science research. Recommendations should be regularly disseminated with the expectation that the epilepsy community will provide feedback and commentary regarding new and appropriate directions for the discovery process.
Appendix A

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