

# New strategies for the identification of drugs to prevent the development or progression of epilepsy

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## Abstract

During the last decade, several new antiepileptic drugs (AEDs) have been introduced in Europe, the United States, or other parts of the world. Although the antiepileptic efficacy of these drugs is not superior to that of older AEDs, some of the new drugs offer advantages in terms of improved tolerability, ease of use, and reduced interaction potential with other drugs. However, the new AEDs have only a modest impact on patients with refractory epilepsies, so that about one third of patients with epilepsy continue to have seizures with current pharmacotherapies. Thus, there is a continuing need for new medical therapies in epilepsy. During the Workshop on “New Horizons in the Development of Antiepileptic Drugs” (November 28–29, 2001, Philadelphia, PA), one topic dealt with the critical re-evaluation of previous preclinical strategies for the discovery and the development of new AEDs. The discussion of this session, which was chaired by the authors, is summarized in this article. Main issues of the discussion were whether epilepsy is a progressive disease and whether refractory epilepsy is preventable, the use of acute versus chronic animal models in the discovery and development of new AEDs, models for drug-resistant epilepsy, mechanisms of drug resistance, alterations in adverse effect potential of AEDs by epilepsy, and advances in pharmacogenomics and our understanding of pharmacologic responsiveness in epilepsy. Overall, it was felt that the current preclinical strategies for the discovery and development of new AEDs have to be redefined in order to identify agents that are clearly superior to current medications. © 2002 Elsevier Science B.V. All rights reserved.

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## 1. Introduction

Epilepsy treatment has advanced dramatically in the last decade, with the introduction of several

new antiepileptic drugs (AEDs) and the marketing of improved formulations of older medications. Nevertheless, neurologists still have no effective way of preventing the development of epilepsy in patients at risk, for example, after brain injury or stroke (Temkin et al., 2001) or in the progressive childhood epilepsies. Such risk factors are present in as many as one-third to one-half of persons with seizure disorders. Since epilepsy is a common

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condition, affecting 1–2% of the population, failure to prevent the development of epilepsy in those individuals who are known to be at risk is a significant lost opportunity for the health care system that has enormous economic and social consequences.

## 2. Epileptogenesis and pharmacoresistance

Current AEDs were developed on the basis of their ability to protect against seizures in animal models. Their utility in reducing the incidence of seizures for many patients with epilepsy is unquestioned. However, there is no evidence that any of the current medications provides a cure or improves the course of the disease (Schmidt, 2002). Specifically, successfully treated patients have a high likelihood of relapse following the discontinuation of medication (Specchio et al., 2002; Berg and Shinnar, 1994) and early treatment does not alter the chances of long-term remission (Musicco et al., 1997). Moreover, trials to date have not shown that AED prophylaxis is useful in preventing the delayed development of epilepsy after head injury (Temkin, 2001). ‘Epileptogenesis’ is generally considered to be the process by which the brain is altered so that there is a propensity for recurrent spontaneous seizures. In the broader sense, however, epileptogenesis encompasses the development of the phenomenon of ‘pharmacoresistance’, in which epilepsy is difficult to treat as a result of neurobiological changes that result in reduced drug sensitivity. Currently available AEDs do not seem to be antiepileptogenic. This could be due to the fact that the current agents act in mechanistically inappropriate ways to prevent disease progression. Indeed, even if kindling in animals does not fully model human epilepsy, it is clear that some AEDs are able to block kindled seizure expression without affecting kindling development (e.g. carbamazepine, oxcarbazepine, lamotrigine, AMPA receptor antagonists; Schmutz et al., 1988; Postma et al., 2000; Rogawski et al., 2001). We will need to understand the cellular and molecular mechanisms involved in disease progression and evaluate drugs in models

that allow assessment of the drug’s ability to prevent epilepsy development, not just suppress seizures. Kindling is an example of such a test system, but it is not clear that it is relevant to any form of progressive human epilepsy.

In addition to a better understanding of mechanisms of epileptogenesis, we need greater insight into the brain excitability mechanisms that account for pharmacoresistance. Some progress has been made along these lines (Heinemann et al., 1994; Löscher, 1997; Vreugdenhil, and Wadman, 1999), but we do not have all the answers. Indeed, the fact that epileptic patients with resistance to one AED are usually also resistant to other AEDs with different molecular mechanisms of action argues against the idea that pharmacoresistance is due to changes in any specific drug target (Jeub et al., 2002). Rather, it may represent a more general and universal phenomenon. Nevertheless, the concept of pharmacoresistance—and the clinical designations ‘non-responder’, ‘refractory’ and ‘medically intractable’—are not well defined. Some difficult-to-treat patients may truly be resistant to available AEDs whereas others would respond if the doses could be increased (which may not be possible, because of side effects).

If pharmacoresistant epilepsy is neurobiologically distinct from easy-to-treat epilepsy, the pharmacoresistant state could evolve progressively from easy-to-treat epilepsy (‘secondary pharmacoresistance’), or could occur *de novo* as non-progressive pharmacoresistant epilepsy (‘primary pharmacoresistance’). In either case, we will need to identify the mechanisms involved and this may lead to clues that can be applied in drug development. We will likely need new *in vitro* test systems and animal models for drug identification. In addition, it will probably be necessary to use radically different patient selection criteria and trial designs to prove the efficacy of such agents. In fact, it is paradoxical that new drugs are often evaluated in subjects who are to some extent pharmacoresistant since individuals with easily treatable seizures do not often enter clinical trials. Yet, these new drugs have failed to make a substantial impact on the fraction of patients experiencing full seizure control.

### 3. Implication for clinical practice

What are the clinical unmet needs? There is an urgent need for diagnostic and surrogate markers that can help predict which patients will develop epilepsy after an insult so as to define who needs prophylaxis. Alternatively, it might be possible to identify markers for those persons who will likely be able to repair or compensate for the brain damage without developing epilepsy. We also need to reliably define patients at risk for drug resistance. Seizures can be fully controlled in about 25% of patients with mesial temporal lobe epilepsy and hippocampal sclerosis; the other 75% with seemingly identical lesions require surgery. How can we identify those patients who will not respond to drugs? Several factors make this a significant challenge. Ten percent of patients with chronic epilepsy may eventually respond when another drug is chosen, indicating that drug-resistance is not always absolute. Moreover, the state of drug resistance may be reversible. Thus, after epilepsy surgery, AED therapy may be highly effective in patients who were formerly intractable (Schiller et al., 2000). Conversely, 6% of patients who at one time responded to a drug with complete seizure control may have a relapse that cannot be controlled again by restoration of the previous drug treatment. This suggests that, at least in some patients, drug resistance may resurface or develop *de novo* after an extended period of complete seizure control.

Another important research question is to determine the optimal time to initiate treatment in an at-risk individual. Neurologists typically prescribe a course of potentially lifelong AED therapy after a patient's first or second seizure. This may be far too late. Indeed the failure of clinical trials seeking to demonstrate that AEDs have a beneficial effect on disease course may not be due to the inadequacy of the drugs, but rather to the fact that they were given at the wrong time. If disease progression is to be altered, in some situations therapy may need to start very early, long before the first seizure. As the genetic bases of various types of idiopathic epilepsy are elucidated, it could very well be practical to institute prophylactic antiepileptogenic therapy in high-risk indi-

viduals based upon their genotypes early in life before the first seizure.

### 4. Conference summary

In the workshop on 'New Horizons in the Development of Antiepileptic Drugs' (November 28–29, 2001, Philadelphia, PA), one of the sessions (chaired by the authors) dealt with new strategies for the identification and development of AEDs that prevent the evolution of the epileptic process and are effective in the treatment of pharmacoresistant epilepsies. There were seven talks within this session, followed by a general discussion. A summary of each presentation and the main discussion points follows.

In his plenary talk, Steven Schachter ("Current antiepileptic drugs are anti-ictal rather than anti-epileptic") noted that despite good evidence that current AEDs protect against seizures in humans (at least for the majority of patients) and that some may be able to block or prevent epileptogenesis in animal models of temporal lobe epilepsy such as kindling, there is currently no definite proof that any exhibit antiepileptogenic effects, although they may in fact be antiepileptogenic. He concluded by saying that, "absence of proof is not proof of absence". Michael Rogawski suggested that a uniform terminology ought to be adopted to clarify thinking and facilitate communication, with the designation 'antiepileptogenic' used in reference to a treatment that prevents the development or progression of epilepsy. (Future 'antiepileptogenic drugs' could perhaps be designated AGDs.) In contrast, 'antiepileptic' is the common term for treatments that protect against seizures (i.e. provide symptomatic relief), and because of its widespread use, ought to be retained for that purpose with the understanding that there is no implication that such treatments alter the course of the disease. The designation 'anticonvulsant drug' would seem to be fading from usage, and rightly so, since many seizures are not convulsive in nature. A disadvantage to the use of the term AED is that some persons with epilepsy may feel that it is stigmatizing.

A key issue raised during the discussion of Schachter's talk is what endpoints are appropriate in clinical studies of antiepileptogenic drugs. Is counting seizures sufficient or should seizure severity be considered or should there be some other outcome measure? Questions were also raised regarding the relationship between anti-seizure and antiepileptogenic activity, the optimum duration of preventive treatment, the ideal study design to show antiepileptogenesis, and the ideal candidate drug for such a study. No definitive answers could be given. Also, it was noted that the pathophysiological mechanisms underlying epileptogenesis may differ depending upon the type of insult—brain injury, infection, status epilepticus or genetic defect. Accordingly, Uwe Heinemann suggested that specific models of epileptogenesis will need to be developed for each of the key causes of epilepsy. Kindling has its merits but other chronic models are needed in the search for disease-modifying drugs. In particular, models are needed of cortical dysplasia, which is one of the major antecedents of epilepsy. Models of chronic epilepsy associated with head trauma or stroke would also be of great value. Attempts to develop such models have been largely unsuccessful, because epilepsy only occurs in a fraction of the subjects (as in the human situation), there is a low incidence of seizures when epilepsy does occur, and there is often considerable latency (up to 1 year) between the initial insult and the onset of seizures. There is a need for more widespread use of systems to monitor animals with experimental epilepsy like those in clinical epilepsy monitoring units. In addition, models are needed in which to test the ability of drugs to stop or reverse the associated development of cognitive and behavioral problems.

## **5. Models of epileptogenesis**

The next four talks considered specific models for the evaluation of drugs with antiepileptogenic activity. Dan McIntyre discussed kindling and concluded that this model provides important insights into what is not necessary for development of spontaneous seizures, since epilepsy occurs in

kindled animals in the absence of any severe brain damage (although there is marked activation of astrocytes). He showed data demonstrating that rats can be separated into substrains that exhibit fast and slow kindling, and he suggested that differences in seizure propagation pathways and local network properties could account for the differences in kindling rates. By continuing kindling stimulation until spontaneous seizures occur in the fast and slow kindlers, it may be possible to generate two groups of animals with different epileptogenic susceptibilities that could be used for drug evaluation. MacIntyre further discussed intriguing similarities between the behaviors exhibited by fast kindling rats (deficits in attention, learning problems, impulsivity and relative hyperactivity) and the symptoms of human attention deficit disorder (ADHD), pointing out that 20% of children with ADHD have epileptic seizures.

Joao Leite discussed how pilocarpine and kainate can be used to develop models of temporal lobe epilepsy that may be of value in the search for anticonvulsant and antiepileptogenic drugs. Both drugs induce status epilepticus that leads—if the animals survive—to a state of chronic limbic seizures; how closely these seizures mimic complex-partial seizures in humans was debated. These models are less labor intensive than electrical kindling, and they can be used in young animals to address possible developmental issues. A major concern with these models is that spontaneous seizures occur infrequently and it may be difficult to discern subtle seizures, so that the determination of the incidence of seizures is problematic and it is hard to determine whether a treatment is effective. Moreover, there can be high intra- and interindividual variability in seizure frequency. This may make some research studies more difficult, but can at the same time be viewed as a potentially favorable characteristic since clinical epilepsy also shows such variability. It was noted that the brain lesions typical of temporal lobe epilepsy do not occur in the pilocarpine model, although this may depend on the duration of antecedent episode of status epilepticus. Unfortunately, at present, there are almost no data on the pharmacological sensitivity of the spontaneous recurrent seizures in these models (because

of the inherent difficulty of monitoring seizures over long periods of time), so that the clinical validity of the models is uncertain. Several discussants pointed out possible differences between the pilocarpine and kainate models. While status epilepticus is the initiating event in both models, the mechanisms of seizure induction are different, so that there could be different mechanisms of epileptogenesis. In support of this idea it was noted that kainate- and pilocarpine-treated animals are dramatically different in terms of their interictal ‘personalities’ and behaviors.

Claude Wasterlain (‘Intermittent Perforant Path Stimulation and Other Electrical Models of Self-sustaining Status Epilepticus’) discussed pharmacological studies with neuropeptides in a model of chronic spontaneous seizures following status epilepticus induced by electrical stimulation of the perforant path. He supported the view that the evaluation of antiepileptogenic compounds should involve models with spontaneous seizures. In the discussion, it was pointed out that drug dosage and time of administration are critical factors when testing drugs for their antiepileptogenic potential. Indeed, further work needs to be done in the status epilepticus models to define the time window during which epileptogenesis occurs and is potentially amenable to treatment.

Jeffrey Noebels (‘Genetic Models of Epilepsy’) reviewed the 53 mouse genes in which mutations have been associated with an epileptic phenotype. However, he noted that there is little information on the AED pharmacology of the mouse mutants, and none of the mutants have as yet been evaluated for pharmacoresistance. In response to a question asking about the uses of the mouse mutants and the possibility of creating new genetic models for specific purposes, he suggested that it would be desirable to develop models for AED drug evaluation, pharmacokinetic studies and the identification of drugs active in pharmacoresistant epilepsies. With the increasing recognition that some epilepsies may be related to mutations in ion channel genes (that is, are ‘channelopathies’), Giuliano Avanzini and Michael Rogawski saw a future for developing drugs that are specifically designed to correct or balance the ion channel defects, as is already beginning to occur

in cardiology (Rogawski, 2000). It was pointed out that the increased understanding of the molecular pathophysiology of idiopathic epilepsies is providing new opportunities for the development of mechanism-specific therapies.

## 6. Status of the current models

Wolfgang Löscher’s talk (‘Results from Drug Testing in Kindling and Different Models with Spontaneous Recurrent Seizures’) about differences in the pharmacology of acute and chronic epilepsy models elicited an animated discussion. Löscher provocatively questioned the predictive value of routine screening tests, including the maximal electroshock (MES) and pentylenetetrazole (PTZ) models, which are commonly used in AED development. He pointed out that the MES test often fails to identify drugs that are clinically effective in treating partial seizures (such as vigabatrin, tiagabine, and levetiracetam) and that it does not distinguish between efficacy in the treatment of primary and secondarily generalized tonic-clonic (GTC) seizures. Moreover, the MES test is not a good model for the identification of drugs for pharmacoresistant epilepsies. Indeed, phenytoin does not exhibit reduced MES activity in rats that have been selected for phenytoin resistance in the kindling model, suggesting that the MES test does not interrogate cellular mechanisms that play a role in pharmacoresistance. Löscher further noted that the PTZ test is often considered a model predicting activity against generalized absence seizures and suggested that, because of considerable contrary evidence, the PTZ test should be discarded. (Some newer AEDs such as lamotrigine are efficacious in human absence epilepsy but are inactive in the rodent PTZ test, whereas other drugs such as phenobarbital, vigabatrin and gabapentin have no efficacy against absence seizures but are protective in the PTZ model.) Other models, including genetic absence epilepsy rats from Strasbourg (GAERS), the lethargic mouse or the  $\gamma$ -hydroxybutyric acid rat model may have greater predictive value (see also Löscher and Schmidt, 1994). Overall, Löscher argued that chronic epilepsy models in which

animals exhibit long term enhanced seizure susceptibility and spontaneous seizures are preferred to acute models such as the MES and PTZ tests, in which normal animals are induced to have seizures. Michael Rogawski agreed that chronic models may have greater ‘face validity’ than the acute models and can potentially identify AEDs that are missed by the acute models, as in the situation with levetiracetam, which is inactive in both the MES and PTZ tests. However, Rogawski defended the MES test saying that it has been validated time and time again as predicting clinical efficacy in the treatment of partial seizures (although competitive NMDA receptor antagonists represent an important exception as they are highly effective in this model, but do not seem to be clinically effective in partial seizures; see Löscher and Rogawski, 2002). The MES test has a high throughput and is very reproducible between laboratories. It has proven its worth since it was responsible for the identification of the most widely used established AEDs and also many of the new drugs. Therefore, Rogawski argued that the MES test continues to be a useful component of a panel of screening tests for AED identification. Rogawski also noted that the MES test should not be considered a model that specifically predicts efficacy in the treatment of GTC seizures. Confidence in the MES test as a tool in AED development derives largely from its demonstrated value in predicting efficacy in the treatment of partial seizures, which represent the main category of seizures included in the large-scale clinical trials required for drug registration. Of course, this does not mean that drugs that are inactive in the MES test (such as vigabatrin, tiagabine and levetiracetam) won’t have activity against partial seizures (these drugs obviously do). Also, it is probably the case that most if not all of the AEDs with demonstrated efficacy in the treatment of partial seizures, are also effective against primary GTC seizures, although this is difficult to prove, because of the practical difficulty in distinguishing primary from secondarily generalized GTCs. Finally, Rogawski reminded the audience that the MES test does not only detect AEDs that act by a sodium channel blocking mechanism; glutamate receptor antagonists are also highly

effective in this model. It cannot be assumed that a novel chemical entity that is effective in the MES test necessarily acts in an identical fashion to other sodium channel anticonvulsants, or even that it acts on sodium channels at all. Therefore, it is not the case that the MES test will only identify ‘me-too’ drugs that duplicate currently available AEDs. Turning to the PTZ test, Rogawski argued that it is premature to abandon this model. He pointed out that the PTZ test continues to be a useful high-throughput screening tool for identifying potential AEDs (many of the old and new drugs are active in this model), but agreed that it cannot anymore be considered a model that predicts efficacy in the treatment of generalized absence seizures. There was a general consensus that any single model, including the MES test, may miss effective compounds for easy-to-treat epilepsy and, perhaps more importantly, those that are potentially useful in the treatment of drug-resistant epilepsy. Therefore, a battery of tests is necessary and it may be worthwhile to continue testing a compound even if it fails in the initial screening tests, although there may be practical limitations in the extent that any one compound can be scrutinized. In this regard, it was pointed out that a systematic evaluation should be performed of the enormous database developed from the animal testing of over 21 000 chemical compounds by the Anticonvulsant Drug Development Program of the National Institute of Neurological Disorders and Stroke, with attention to the possibility that some of the substances that failed in the test battery might still be of utility, perhaps even as antiepileptogenic agents.

Several discussants lamented the lack of a clinically validated animal model of human pharmaco-resistant epilepsy. The identification of such a model is a high priority. Possible candidates are amygdala and corneal kindling, genetic models, and the 6-Hz electroshock model in mice or rats (Barton et al., 2001). An important problem is the lack of a ‘positive control’ in studies aiming to identify a drug effective in patients with pharmaco-resistant epilepsy, which was referred to by Robert Post as ‘contingent inefficacy’. The only way around this problem would seem to be the serendipitous discovery of the ‘magic bullet’ or

the development of a better understanding of pharmacoresistance. Given the deficiencies of current drug screening models, some members of the audience proposed that new models ought to be developed based upon known causes of human epilepsy, such as brain trauma, ischemia or infection. Others suggested that human brain tissue should be used.

Fernando Lopes da Silva ('Abnormal Plasticity of Limbic Cortex Leading to Epileptogenesis') described data showing that in the status epilepticus models, about 70% of rats have a progressive course, with an increase in spontaneous seizure frequency over time, whereas the other 30% do not show any progression. These subgroups may be useful to study mechanisms involved in epilepsy progression and to evaluate whether drugs can modify the disease course. Following an episode of status epilepticus in rats, there is an increase in hippocampal neonatal-type sodium channels, which may be less sensitive to drugs than are normal adult-type channels. In human brain tissue obtained during resective surgery, sodium channels exhibit reduced sensitivity to carbamazepine in focal but not extrafocal areas. Thus, surgical resection of focal tissue may render a patient sensitive to the effects of an AED like carbamazepine, because the pharmacoresistant epileptic tissue is removed. In the discussion it was pointed out that development of 'juvenile features' in epileptic tissue occurs after different initiating events leading to epilepsy, such as status epilepticus or head trauma.

## 7. Conclusion

During the general discussion that followed the presentations, optimism was expressed that modern approaches in molecular medicine, including genome sequencing and expression analysis with gene arrays, would eventually allow the identification of persons who are at risk for the development of epilepsy and provide approaches to defining which drug is appropriate for each individual patient. At the same time, advancements in the neurobiology of epileptogenesis and drug resistance would allow the identification of new

drug molecules to prevent epilepsy development and treat pharmacoresistant patients. It was recognized, however, that in recent years there has been diminishing interest on the part of industry to devote resources to epilepsy drug development. Appreciation of the opportunities that epilepsy drugs offer for other clinical indications with larger markets, such as bipolar disorder, chronic pain or anxiety, could turn this trend around. Nevertheless, there is a continuing need for the involvement of academia and government in epilepsy research and therapy development.

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