Discovery of Antiepileptic Drugs

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Summary: Since 1993, the Anticonvulsant Drug Development Program has contributed to the successful development of nine clinically effective drugs for the symptomatic treatment of epilepsy. These include felbamate (1993), gabapentin (1994), lamotrigine (1994), fosphenytoin (1996), topiramate (1996), tiagabine (1997), levetiracetam (1999), zonisamide (2000), and oxcarbazepine (2000). Despite the apparent success of the current discovery process, a significant need persists for more efficacious and less toxic antiepileptic drugs (AEDs). This is particularly true for patients whose seizures remain refractory to the currently available AEDs. This chapter will review the current process for AED discovery employed by the Anticonvulsant Drug Development Program at the University of Utah and other laboratories working toward the common goal of discovering better therapeutic options for patients living with epilepsy. It will discuss some of the inherent advantages and limitations of the primary animal models employed, while offering insight into potential future directions as we seek to better understand the pathophysiology underlying acquired epilepsy, therapy resistance, and epileptogenesis. **Key words:** AED discovery, animal models, seizure, epilepsy

INTRODUCTION

The discovery of novel antiepileptic drugs (AEDs) relies upon the preclinical employment of animal models to establish efficacy and safety prior to the introduction of the AEDs in human volunteers. Since 1974, the National Institute of Neurological Disorders and Stroke (NINDS) has facilitated the development of novel chemical entities for the symptomatic treatment of epilepsy. The efforts of the NINDS have largely been carried out by the Anticonvulsant Screening Program, which has accessioned over 27,000 investigational AEDs from academic and pharmaceutical chemists worldwide. Through a contract with the Anticonvulsant Drug Development (ADD) Program of the University of Utah, potential compounds undergo an initial identification, characterization, and differentiation of anticonvulsant efficacy and toxicity using a battery of well defined animal models.[1–4] The screening protocol of the ADD program is constantly evolving to include well-characterized models that might provide more clinically relevant information. While thousands of new chemical entities will enter the initial screening process, very few compounds will progress beyond the early identification phase and proceed to advanced testing. Even fewer will proceed to clinical testing. Clearly, the more predictive the animal model for any given seizure type or syndrome, the greater the likelihood that an investigational AED will demonstrate efficacy in human clinical trials.

THE "IDEAL" MODEL SYSTEM

The National Institutes of Health (NIH)/NINDS/American Epilepsy Society (AES) Models II Workshop, held in 2002, described the "ideal" epilepsy model as one that reflects similar pathophysiology and phenomenology to human epilepsy. Seizures should evolve spontaneously after a postinsult latent period or in a developmental time frame consistent with the human condition. Furthermore, the ideal model should display a pharmacological profile that is resistant to at least two of the existing AEDs.[5] Finally, the ideal model would be amenable to high-throughput screening. Given the highly heterogeneous nature of seizure disorders in humans, the complexity of the seizure phenotypes, and the syndromes involved, the reality is that it is highly unlikely that any one animal model will ever predict the full therapeutic potential of an investigational AED. Therefore, investigational AEDs are currently evaluated in a battery of

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TABLE 1. *Correlation Between Anticonvulsant Efficacy and Clinical Utility of the Established and Second-Generation AEDs in Experimental Animal Models*

	Clinical Seizure Type			
Experimental Model	Tonic and/or Clonic Generalized Seizures	Myoclonic/Generalized Absence Seizures	Generalized Absence Seizures	Partial Seizures
MES (tonic extension)*	CBZ, PHT, VPA, PB [FBM, GBP, LTG, TPM, ZNS]			
scPTZ (clonic seizures)*		ESM, VPA, PB†, BZD [FBM, GBP, TGB†, VGB†]		
Spike-wave discharges (absence seizures)‡			ESM, VPA, BZD [LTG, TPM, LVT]	
Electrical kindling (focal seizures)				CBZ, PHT, VPA, PB, BZD [FBM, GBP, LTG, TPM, TGB, ZNS, LVT, VGB]
6 Hz (44 mA)§				VPA [LVT]

[ ] Second-generation AEDs.
BZD = benzodiazepines; CBZ = carbamazepine; ESM = ethosuximide; FBM = felbamate; GBP = gabapentin; LTG = lamotrigine; LVT = levetiracetam; MES = maximal electroshock; PB = phenobarbital; PHT = phenytoin; scPTZ = subcutaneous pentylenetetrazol; TGB = tiagabine; TPM = topiramate; VGB = vigabatrin; VPA = valproic acid; ZNS = zonisamide. *Data summarized from White et al.[1] †PB, TGB, and VGB block clonic seizures induced by sc PTZ but are inactive against generalized absence seizures and may exacerbate spike wave seizures. ‡Data summarized from Snead[36]; Marescaux and Vergnes[37]; Hosford et al.[38]; and Hosford and Wang.[22] §Data summarized from Barton et al.[16]

syndrome-specific model systems. As specific models are developed (and the drugs they identify are validated clinically), they are integrated into the existing discovery process to better identify more effective antiseizure and potentially antiepileptic therapies. Moving beyond the symptomatic treatment of epilepsy, the goal of most basic and clinical scientists in epilepsy research is to identify therapies capable of preventing, delaying, or modifying the disorder.

THE PRECLINICAL AED DISCOVERY PROCESS

A number of animal models have demonstrated utility in the search for more efficacious and more tolerable AEDs. In fact, the models employed in the early phase of AED discovery are highly predictive of subsequent efficacy in easy-to-manage generalized and partial epilepsy. However, because approximately 25-40% of patients with partial epilepsy fail to achieve satisfactory seizure control, one could easily argue that these early discovery models lack sufficient predictability for "therapy-resistant" seizures.[6] This does not negate the value of new drugs identified by the current AED discovery process. Rather, most agree that the second-generation AEDs have provided significant benefits to patients with partial epilepsy in the form of improved efficacy, better tolerability, more favorable pharmacokinetics, and greater long-term safety (TABLE 1).

The University of Utah Anticonvulsant Drug Development Program employs three primary screens in their initial identification studies: the maximal electroshock (MES), the subcutaneous pentylenetetrazol (scPTZ), and the 6 Hz psychomotor seizure tests. Each of these evoked seizure models provides valuable information regarding the potential anticonvulsant spectrum of an investigational AED.

The MES and scPTZ Tests

The MES and scPTZ seizure models continue to represent the two most widely used animal seizure models employed in the search for new AEDs.[1] The current era of AED discovery was introduced by Putnam and Merritt[7] in 1937 when they identified the anticonvulsant potential of phenytoin (PHT) using the MES model. The subsequent success of PHT in the clinical management of generalized tonic–clonic seizures and partial epilepsy provided the validation necessary to consider the MES test as a reasonable model of human generalized tonic–clonic seizures. Everett and Richards[8] demonstrated that both trimethadione and phenobarbital, but not PHT, were able to block seizures induced by the $GABA_A$-receptor antagonist PTZ. Soon thereafter, Lennox demonstrated that trimethadione was effective at attenuating petit mal (i.e., absence epilepsy) attacks but was ineffective in treating or worsening grand mal seizures (i.e., generalized tonic– clonic seizures).[9] The clinical success of trimethadione and its ability to block PTZ-induced

threshold seizures provided sufficient evidence to establish the PTZ test as a model of generalized absence seizures.

The pharmacological profile of the MES and scPTZ tests does provide some insight into the potential clinical utility of drugs that are found to be active in one or both of these tests. For example, the pharmacological profile of the MES test supports its utility as a predictive model for human generalized tonic–clonic seizures. In contrast, the lack of any demonstrable efficacy by tiagabine, vigabatrin, and levetiracetam in the MES test argues against the utility of this test as a predictive model of partial seizures. Consistent with this conclusion is the observation that NMDA antagonists are very effective against tonic extension seizures induced by MES but have been shown to be ineffective in patients with partial seizures.[10]

The positive results obtained in the scPTZ seizure test were historically considered suggestive of potential clinical utility against generalized absence epilepsy, based largely on the finding that drugs active in the clinic against spike-wave seizures (e.g., ethosuximide, trimethadione, valproic acid, the benzodiazepines) were effective at blocking clonic seizures induced by scPTZ. In contrast, sodium channel antagonists such as phenytoin and carbamazepine are ineffective against spike-wave seizures and inactive in the scPTZ test. Based on this argument, one would predict that phenobarbital, gabapentin, and tiagabine should all be effective against spike-wave seizures and lamotrigine should be inactive against spike-wave seizures. However, clinical experience has demonstrated that this is an invalid prediction, because barbiturates, gabapentin, and tiagabine all aggravate spike-wave seizure discharge, and lamotrigine is effective against absence epilepsy. As such, the overall utility of the scPTZ test in predicting activity against human spike-wave seizures is limited and any positive results in the scPTZ test should be corroborated by positive findings in other models of absence before drawing conclusions on potential clinical utility against spike-wave seizures.

One might then ask what, if any, advantages the MES and scPTZ tests provide in the current AED discovery process. First, both tests provide some insight into the ability of a given drug to penetrate the blood-brain barrier and exert a CNS effect. Secondly, both models are nonselective with respect to mechanism and therefore are well suited for screening anticonvulsant activity, as neither model assumes that the pharmacodynamic activity of a particular drug is dependent on its molecular mechanism of action. Finally, both model systems display clear and definable seizure endpoints and require minimal technical expertise. These properties make them ideally suited to screen large numbers of chemically diverse entities. Unfortunately, beyond being amenable to high-volume screening, the MES and scPTZ tests both fail to meet any of the remaining criteria described for the ideal model system.

Because the MES and scPTZ tests are conducted in "normal" rodents, another important consideration is that the pharmacology of AEDs can be affected by the disease state. In other words, there is no guarantee that identified AEDs will be equally effective in "pathologically abnormal" rodents. For example, the MES and scPTZ tests failed to identify the anticonvulsant activity of levetiracetam. Subsequent investigations demonstrated that levetiracetam was active in "pathologically abnormal" models of partial and primary generalized seizures.[11–15] In this regard, levetiracetam appears to represent the first "truly" novel AED identified in recent years. The identification, and subsequent development and launch of levetiracetam as an efficacious AED for the treatment of partial seizures, demonstrates the need for flexibility when screening for efficacy and the need to incorporate levetiracetam-sensitive models into the early evaluation process.

The 6 Hz seizure test

The case of levetiracetam exemplifies the continuing need to identify and characterize new screening models so as to minimize the risk of missing other potentially novel AEDs; this is why the ADD program at the University of Utah utilizes the 6 Hz psychomotor seizure model in its early identification studies.[16,17] The low-frequency (6 Hz), long-duration (3 s) corneal stimulation paradigm was developed in hopes of validating the 6 Hz model as a screening test for partial seizures; however, the pharmacological profile was not consistent with clinical practice[18] because phenytoin was found to be inactive in the 6 Hz seizure test. Given the observation that the 6 Hz model was no more predictive of clinical utility than the other models available (the MES and scPTZ tests), it was virtually abandoned. Subsequent investigations in our laboratory confirmed the relative insensitivity of the 6 Hz test to phenytoin and extended the observation to include carbamazepine, lamotrigine, and topiramate.[16] The relative resistance of some patients to phenytoin and other AEDs in the clinical setting today, and the lack of sensitivity of the MES and scPTZ to levetiracetam, prompted additional studies to re-evaluate the 6 Hz seizure test as a potential screen for therapy-resistant epilepsy.[16] Results from these studies suggest that the 6 Hz seizure test may offer some advantage over the MES and scPTZ tests, because the pharmacological profile of the 6 Hz test has differentiated itself from other acute seizure models.[16] For example, as the stimulus intensity is increased from the CC_{97} (convulsive current required to evoke a seizure in 97% of the mice tested) to twice the CC_{97}, the pharmacological profile shifts from being relatively nondiscriminating to being highly dis-

TABLE 2. *Effect of Stimulus Intensity on the Anticonvulsant Efficacy of Phenytoin, Lamotrigine, Ethosuximide, Levetiracetam, and Valproic Acid in the 6 Hz Seizure Test**

	ED50 (mg/kg, intraperitoneal) and 95% CI†		
Antiepileptic Drug	22 mA	32 mA	44 mA
Phenytoin	9.4 (4.7–14.9)	>60	>60
Lamotrigine	4.4 (2.2–6.6)	>60	>60
Ethosuximide	86.9 (37.8–156)	167 (114–223)	>600
Levetiracetam	4.6 (1.1–8.7)	19.4 (9.9–36.0)	1089 (787–2650)
Valproic acid	41.5 (16.1–68.8)	126 (94.5–152)	310 (258–335)

*From Barton et al.[16]; with permission. †Confidence interval (CI) shown in ( ).

criminating (see TABLE 1). At the CC_{97} (22 mA), all of the AEDs tested (phenytoin, lamotrigine, ethosuximide, levetiracetam, and valproic acid) are active at doses devoid of behavioral toxicity. At a current intensity 1.5 times the CC_{97} (32 mA), the 6 Hz seizure is resistant to phenytoin and lamotrigine, but sensitive to ethosuximide, levetiracetam, and valproic acid. As the stimulus current is further increased to 44 mA, the 6 Hz seizure becomes insensitive to ethosuximide and less responsive to levetiracetam and valproic acid. As such, the 6 Hz test may represent a potential therapy-resistant model, where seizures can be acutely evoked in normal mice. Such a model would provide a rather inexpensive alternative to the extremely labor-intensive and expensive chronic models such as kindling.

Differentiation of anticonvulsant activity

Once the efficacy of an investigational AED is established using either the MES, scPTZ, or 6 Hz seizure test, a battery of tests are performed to characterize the anticonvulsant potential of an active investigational AED. These include assessing the ability of the investigational AED to block audiogenic seizures in the Frings audiogenic mouse, limbic seizures in the hippocampal kindled rat and acute clonic seizures induced by the $GABA_A$ receptor antagonist bicuculline and the Cl^--channel blocker picrotoxin.[1–3] This approach serves to define whether an active compound possesses a narrow or broad spectrum of activity and provides the sponsor with a sense of how their compound compares with prototype "marketed" compounds.

Of the multitude of tests that one might elect to conduct, the kindled rat model is the only chronic model currently employed by a majority of AED discovery programs. The kindled rat model offers perhaps the best predictive value of all of the tests described thus far, because it is the only model that adequately predicted the clinical utility of both first- and second-generation AEDs, including tiagabine and vigabatrin (see TABLE 1 for review), as well as the lack of clinical efficacy of NMDA antagonists.[19] One might wonder why the kindled rat is not a primary screen rather than a secondary screen for the early identification and evaluation of novel AEDs. The answer is primarily one of experimental logistics. Any chronic model such as kindling is extremely labor intensive and requires adequate facilities and resources to surgically implant the stimulating–recording electrode, as well as to kindle and house sufficient rats over a chronic period of time. Furthermore, unlike the acute seizure models, the time required to conduct a drug study with a chronic model far exceeds the time required to conduct a similar study with any of the acute seizure models (e.g., MES, scPTZ, or 6 Hz seizure tests), thereby severely limiting the number of AEDs that can be screened in a timely manner.

It is important to keep in mind that seizures are the ultimate clinical expression of any given patient's epileptic disorder and, thus, prevention of seizures as an endpoint for any initial AED discovery program is not inappropriate. As such, the utilization of the MES, scPTZ, or any other acute seizure model to screen a structural series of candidate AEDs in order to identify and optimize a lead compound should be considered acceptable. The question of whether the "lead compound" differentiates itself in terms of better tolerability, safety, and efficacy against therapy-resistant seizures will require additional testing in more appropriate model systems before making the transition from animal models to humans (see Rogawski, this issue). The efforts of anticonvulsant discovery programs such as the ADD program have provided an extensive database of information regarding the efficacy and tolerability of various prototype and investigational compounds in a wide variety of models and administration routes.[1,3]

Activity of a test substance in one or more of the electrical and chemical tests described above will provide some insight into the overall anticonvulsant potential of the compound. However, a concern voiced in recent years is that the continued use of the MES and scPTZ tests in the early evaluation of an investigational AED are unlikely to discover those drugs with different mechanisms of action.

When attempting to identify and characterize the overall potential of a candidate AED substance, the importance of employing multiple models cannot be over-

stated. For example, levetiracetam is inactive in the traditional MES and scPTZ tests, yet it demonstrates excellent efficacy in the kindled rat model.[14] Likewise, the efficacy of tiagabine and vigabatrin against human partial seizures was not predicted by the MES test, but by the kindled rat model.[20,21] Furthermore, exacerbation of spike-wave seizures by tiagabine, vigabatrin, and phenobarbital was not predicted by the scPTZ test but by other models (i.e., γ-hydroxybutyrate, genetic absence epilepsy rat from Strasbourg, and the *lh/lh* mouse).[22] These examples demonstrate the importance of evaluating each investigational AED in a variety of seizure and epilepsy models. Only then will it be possible to gain a full appreciation of the overall spectrum of activity for a given investigational drug.

FUTURE OF AED DISCOVERY

As discussed above, the mainstay of most AED discovery programs has been the MES test, the scPTZ test, and the kindled rat. Unfortunately, despite their clinical predictiveness, there still remains a significant unmet need for the patient with "pharmacoresistant" epilepsy. To this end, the identification and characterization of one or more model systems that would predict efficacy in the pharmacoresistant patient population would be a valuable asset for any AED discovery program. As well as being useful for therapy development, the ability to segregate animals on the basis of their responsiveness or lack of sensitivity to a given AED would be useful for attempting to understand the molecular mechanisms underlying pharmacoresistance. In addition to aiding in understanding the mechanism of pharmacoresistance, an animal model of therapy resistance would be an asset for those studies designed to assess whether it is possible to reverse drug resistance, or, potentially, to predict which patients will remit and become pharmacoresistant. Given that most of these questions are extremely difficult to address directly in patients, it is important to continue the efforts to validate the established and newer models as they become available.

In recent years there have been several *in vivo* model systems described that display a phenotype consistent with pharmacoresistant epilepsy (Loscher[23] for review). These include: the phenytoin-resistant kindled rat,[24,25] the lamotrigine-resistant kindled rat,[26–29] the 6 Hz psychomotor seizure model of partial epilepsy,[16] poststatus epileptic models of temporal lobe epilepsy,[30–34] and the methylazoxymethanol acetate *in utero* model of nodular heterotopia.[35] Of particular interest is the finding that the pharmacology of these models tends to better mimic the human condition (e.g., the presence of responders and nonresponders). By testing new drugs in animals that are found to be nonresponsive to existing therapies, we may be able to better predict efficacy in a particular patient population and thereby enrich our chances of identifying the truly novel therapy. This approach, albeit costly and labor intensive, should be considered when attempting to differentiate a new drug from those that are either on the market or currently undergoing clinical trials.

CONCLUSIONS

This review has focused on the present day process employed by the University of Utah Anticonvulsant Drug Development Program to evaluate the anticonvulsant efficacy of an investigational AED submitted to the NINDS Anticonvulsant Screening Project for the symptomatic treatment of epilepsy. The brief overview of the model systems utilized by this program is by no means meant to suggest that this is the only approach that an individual can utilize for anticonvulsant identification, characterization, and differentiation.

In addition to discussing the advantages and limitations of the current discovery process and the various animal model systems currently employed by the ADD program, this review has offered some insight into potential future directions and models that may assist in the discovery of the next truly novel AED. In this regard, there is an ever-pressing need to continue the search for drugs that will be more effective for the patient with therapy-resistant epilepsy. This latter approach will require the identification and characterization of numerous model systems and the subsequent development of a highly efficacious therapy in the "pharmacoresistant" patient population before any recommendations regarding appropriate models of "pharmacoresistance" can be offered.

Lastly, therapeutics designed to modify the course of epilepsy or prevent the development of epilepsy in the susceptible patient will require testing in appropriate animal models. Numerous models of acute status epilepticus display many similarities with the human condition, including pathology, a species appropriate latent period, and the development of spontaneous seizures after the latent period. Among the various syndrome-specific models there are several differences, both subtle and gross, that necessitate their continued evaluation in order to access their validity to the human condition and their appropriateness for therapy discovery. Unfortunately, the true validation of any given model of epileptogenesis will necessitate the development of an effective therapy that prevents or delays the development of epilepsy or secondary hyperexcitability in the human condition and whose activity was successfully predicted by preclinical testing.

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