Title
What Clinical Observations on the Epidemiology of Antiepileptic Drug Intractability Tell Us About the Mechanisms of Pharmacoresistance

Permalink
https://escholarship.org/uc/item/1z28v0dq

Author
Rogawski, Michael A.

Publication Date
2008-07-17

What Clinical Observations on the Epidemiology of Antiepileptic Drug Intractability Tell Us About the Mechanisms of Pharmacoresistance

Michael A. Rogawski, M.D., Ph.D.
Department of Neurology, University of California, Davis, Sacramento, California 95817, U.S.A.

In the past several years, there have been important advances in the clinical epidemiology of antiepileptic drug resistance, as reviewed by Mohanraj and Brodie. It would appear that by and large, intractability is independent of the choice of antiepileptic drug (AED). Many patients will become seizure free on the first agent tried, irrespective of which one their physician decides to pick. Nonresponders to the first drug are in a different category: it is likely that they will continue to have seizures no matter which medicine or combination of medicines is tried. This simple clinical observation puts important constraints on the possible biological mechanisms for pharmacoresistance. In this essay, I consider the implications of the new clinical research for studies on the neurobiological mechanisms of AED intractability.

AEDs Have Many Distinct Cellular Mechanisms of Action

 Clinicians have a wide range of AEDs to choose from. There are 23 distinct chemical entities marketed worldwide for epilepsy therapy. Some of these agents are known to be useful for a limited range of seizure types. For example, ethosuximide is largely exclusively used in childhood absence. Tiagabine, vigabatrin, phenytoin, carbamazepine and oxcarbazepine are mainly useful for partial and primarily generalized seizures. The other agents, including valproate, topiramate, levetiracetam, have broader utility. With very few exceptions, each AED acts in a mechanistically distinct way. This is not the situation in other therapeutic areas. For example, the triptans used to abort migraine attacks all act in a similar fashion as agonists of serotonin 5-HT_{1B} and 5-HT_{1D} receptors; the selective serotonin reuptake inhibitors used to treat depression all block the serotonin transporter; the many statins are all HMG-CoA reductase inhibitors; and the proton pump inhibitors all have the same molecular target. In contrast, each AED generally acts on a unique set of molecular targets. Even when they share the same molecular target, as is the case for AEDs that act on voltage-activated sodium channels, the biophysical details for each drug are sufficiently different that the mechanisms must be considered distinct (Rogawski and Löscher, 2004). For example, there may be important differences in binding rate (Kuo et al., 1997), binding affinity (Kuo and Lu, 1997), on the ability to block open channels (Yang and Kuo, 2002) or effects on persistent sodium current (Stafstrom, 2007) or effects on other ion channels, as is the case for lamotrigine, where modulation of voltage-activated calcium channels may be relevant to its therapeutic activity. Another major class of AED actions relate to interactions with GABA-mediated inhibition. Some drugs, most notably benzodiazepines and phenobarbital, but also felbamate and topiramate, positively modulate $GABA_A$ receptors. The specific details of how each of these agents acts is distinct. For example, benzodiazepines and phenobarbital modulate $GABA_A$ receptors at distinct sites and in different ways. Unlike benzodiazepines, phenobarbital, felbamate and topiramate act on targets other than

GABA$_A$ receptors that likely contribute to therapeutic activity. Vigabatrin inhibits GABA transaminase, whereas tiagabine blocks the GAT-1 GABA transporter; each of these agents affects the dynamics of inhibitory function in dramatically different ways. Other AEDs exert their anticonvulsant action through novel targets. For example, levetiracetam acts through SV2A, a ubiquitous synaptic vesicle protein, whereas gabapentin and pregabalin act through α2δ, a novel presynaptic protein associated with voltage-activated calcium channels (Rogawski and Taylor, 2006; Meldrum and Rogawski, 2007).

Inadequacy of the Target Hypothesis

A number of hypotheses have been proposed to explain AED pharmacoresistance (Schmidt and Löscher, 2005). One major hypothesis is that alterations in the structure or function of the molecular targets through which AEDs act lead to reduced drug activity. However, since diverse AEDs act in so many different ways and on different sets of molecular targets, this so-called "target hypothesis" seems incompatible with the clinical evidence that certain patients are resistant to all available drugs. It is unlikely that all of the targets would become changed in such a way to produce pan pharmacoresistance. There are two forms to the target hypothesis and this argument applies equally well to both. In the conventional form of the target hypothesis, the molecular target—most commonly voltage-activated sodium channels—loses pharmacological sensitivity to AEDs during the acquisition of pharmacoresistance (Vreugdenhil and Wadman, 1999; Remy et al., 2003; Ellerkmann et al., 2003). However, in the studies supporting this hypothesis, the sensitivity to drugs that act on other molecular targets, notably valproate and lamotrigine, was unaffected. The mechanism of action of valproate is poorly understood but is unlikely to relate largely to an interaction with sodium channels. Lamtrigine has a different spectrum of activity than other AEDs and, as noted, acts on calcium channels in addition to sodium channels. Clearly, this resistance mechanism could only apply to AEDs that act largely on the specific target affected. Other challenges to the target hypothesis are discussed by Schmidt and Löscher (2005). A second form of the target hypothesis posits that there are genetically-determined polymorphisms in an AED target that alters AED responsiveness. Indeed, Tate et al. (2005) identified a polymorphism in the SCNA1 sodium channel gene that appeared to confer resistance to carbamazepine and phenytoin, although they subsequently did not replicate the association (Tate et al., 2006). Whether or not a sodium channel polymorphism is associated with pharmacoresistance to drugs that act on sodium channels, clinical AED intractability, in which there is a failure to adequately respond to all available agents, is not explained.

Questions Regarding the Transporter Hypothesis

A leading hypothesis regarding drug resistance in epilepsy is the so-called "transporter hypothesis" which postulates that drug efflux transporters located in the apical membrane of capillary endothelial cells that form the blood-brain barrier limit AED availability to their molecular targets in the brain (Löscher and Potschka, 2005). The best studied transporter is P-glycoprotein (P-gp) but other transporters, including multidrug-resistance–associated proteins (MRPs), could also play a role in pharmacoresistance to

AEDs. Reports that P-pg and members of the MRP family are overexpressed in experimentally induced seizure foci and brain tissue specimens removed during surgery of patients with pharmacoresistant epilepsy have raised the possibility that localized overexpression of transporter proteins accounts for the inability to overcome resistance by increasing the drug dose, since other brain regions would then be exposed to supratherapeutic (toxic) drug concentrations (Tishler et al., 1995; Dombrowski et al., 2001; Aronica et al., 2004). In addition to the observation of increased transporter expression, which could be due the epileptic process itself or the occurrence of seizures, it has been proposed that genetic polymorphisms in a transporter gene could account for increased functional transporter activity. However, none of the proposed associations between transporter genotype and clinical drug response have been replicated (Soranzo et al., 2007; Leschziner et al., 2007ab). In any case the genetic form of the transporter hypothesis seems unlikely since a generalized upregulation of transporter activity could be overcome by increasing the AED dose.

The major weakness of the multidrug transporter hypothesis is the lack of evidence that AEDs are substrates for P-gp or any other human efflux transporter (Rogawski, 2002; Löscher and Sills, 2007). While there is evidence in experimental animals that several commonly used AEDs are transported to some extent by both P-gp and MRPs (Löscher and Potschka, 2005; van Vliet et al., 2006), recent experiments employing transfected cell lines expressing rodent and human efflux transporters have cast doubt that the drugs are truly substrates for the human forms of the transporters (Crowe and Teoh, 2006). Even in mice, the extent to which AEDs are transported by P-gp must be very small as genetic deletion of P-gp does not influence brain uptake of many AEDs (Sills et al., 2002). Indeed, it is apparent that AEDs are not efficiently extruded from brain since all AEDs exhibit CNS side effects, even if they fail to confer adequate seizure protection. Finally, the fact that most AEDs show linear uptake into the brain over a wide range of concentrations calls into question the existence of a saturable transport system that influences the dynamics of AED transport across the blood-brain barrier (Anderson and Shen, 2007).

Does "Inherent Severity" Account for Pharmacoresistance?

A variety of clinical factors are known to be associated with intractability. The most important and well validated of these factors is the frequency of seizures in the period immediately after diagnosis. Several early studies demonstrated that frequent seizures are associated with bad prognosis (Brorson and Wranne, 1987) and that high initial seizure frequency during the period after presentation is an important predictor of seizure intractability (Collaborative Group for the Study of Epilepsy, 1992; Sillanpää, 1993; MacDonald et al., 2000). A recent study confirmed the prognostic implications of high early seizure frequency and also identified several other factors associated with intractability including family history of epilepsy, febrile seizures, traumatic brain injury, recreational drug use, and a history of depression (Hitiris et al., 2007). These results suggest that neurobiological factors related to the occurrence of frequent seizures are associated with intractability. This observation seems logical: if the epilepsy is of a nature that seizures are easy to trigger, the seizures may be more difficult to prevent. AEDs

probably do not act as a switch to turn off the possibility of seizure occurrence; rather, they make it more difficult to trigger a seizure. That is, they raise the threshold for a seizure-inducing stimulus. In most (but not all) animal models in which seizures are induced by a pharmacological or electrical stimulus, raising the intensity of the trigger can overcome the seizure protection conferred by a given dose of an AED. As is the case with a triggered seizure, if seizure susceptibility is inherently high, it may not be possible to prevent seizure occurrence with any nontoxic drug dose. This leads to the concept that there is a degree of inherent severity in any individual epilepsy patient that does not necessarily depend upon the underlying etiology. Rather, for syndromes of similar etiology, the severity can range from mild to severe, just as diabetes or cystic fibrosis can range in disease severity. Indeed, it appears that disease severity can depend upon specific modifier genes, as in the case of a movement disorder in mice linked to a mutation in the $Na_V 1.6$ voltage-activated sodium channel (Buchner et al., 2003). Mice homozygous for the $Na_V 1.6$ mutation (med^J/med^J) exhibit a highly variable phenotype ranging from slowly progressive tremor and dystonia and lifespan >1.5 years to paralysis and death at 1 month of life. Disease severity has been found to depend upon the genetic background, specifically to an unlinked gene (*Scnm1*) that influences the splicing of the mRNA that encodes $Na_V 1.6$. This modifier gene dramatically alters the severity of the neurological syndrome. It seems likely that there are similar modifier effects that alter the severity of epilepsy and overall drug responsiveness.

The concept of genetically determined epilepsy severity implies that severely affected patients are difficult to control from the time of their first seizure and that the occurrence of uncontrolled seizures over time is not the cause of the intractability. Indeed, the wealth of evidence suggests that most cases of epilepsy are not progressive and do not worsen over time as a result of uncontrolled seizures (Berg and Shinnar, 1997; Shorvon and Luciano, 2007). Finally, we note that disease severity need not necessarily be static, but may fluctuate in response to internal factors and environmental influences. For example, in perimenstrual catamenial epilepsy, severity (and drug intractability) is dependent on hormonal fluctuations occurring at the time of menstruation (Rogawski, 2003).

Conclusions

What implications does the "inherent severity" hypothesis have for the development of strategies to overcome pharmacoresistance? While it will always be challenging to treat more severely affected patients, it should not be assumed that seizure freedom is unattainable in such patients. The inherent severity model proposes that there is a continuum in severity so that new AEDs acting on novel molecular targets may offer protection for such patients. Recent data is compatible with this optimistic view. Thus, Callaghan et al. (2007) found that drug refractory patients who have not responded to at least two AEDs do achieve remission at a rate of about 5% per year. In the majority of cases, the remission was associated with the addition or increase in dose of an AED, most commonly lamotrigine or levetiracetam. While insufficient data was available for these authors to conclude that these drugs are more likely to induce remission than other AEDs, it seems plausible that the availability of a broader range of AEDs accounts for the fact that these authors obtained better rates of seizure remission in their intractable patients

than has previously been observed. A variety of new AEDs are currently in development, some of which act in new ways on old targets and others that act on entirely new targets (Rogawski, 2006). We can expect that these new drugs will further benefit patients by having improved side effect profiles, improved pharmacokinetic properties, reduced propensity for drug interactions, less teratogenic potential, an improved spectrum of activity and, most importantly, by their ability to induce seizure remission in some patients previously considered intractable. In the future, if modifier genes can be identified that influence severity in human epilepsies, it may be possible to specifically target the biological mechanisms accounting for greater severity, making seizure control feasible in previously intractable patients.

References

Anderson GD, Shen DD. Where is the evidence that p-glycoprotein limits brain uptake of antiepileptic drug and contributes to drug resistance in epilepsy? Epilepsia 2007;48:2372-2374.

Aronica E, Gorter JA, Ramkema M, Redeker S, Ozbas-Gerçeker F, van Vliet EA, Scheffer GL, Scheper RJ, van der Valk P, Baayen JC, Troost D. Expression and cellular distribution of multidrug resistance-related proteins in the hippocampus of patients with mesial temporal lobe epilepsy. Epilepsia 2004;45:441-451.

Berg AT, Shinnar S. Do seizures beget seizures? An assessment of the clinical evidence in humans. J Clin Neurophysiol 1997;14:102-110.

Brorson LO, Wranne L. Long-term prognosis in childhood epilepsy: survival and seizure prognosis. Epilepsia 1987;28:324-330.

Buchner DA, Trudeau M, Meisler MH. SCNM1, a putative RNA splicing factor that modifies disease severity in mice. Science 2003;30:967-969.

Callaghan BC, Anand K, Hesdorffer D, Hauser WA, French JA. Likelihood of seizure remission in an adult population with refractory epilepsy. Ann Neurol 2007;62:382-389.

Collaborative Group for the Study of Epilepsy. Prognosis of epilepsy in newly referred patients: a multicenter prospective study of the effects of monotherapy on the long-term course of epilepsy. Epilepsia 1992;33:45-51.

Crowe A, Teoh YK. Limited P-glycoprotein mediated efflux for anti-epileptic drugs. J Drug Target 2006;14:291-300.

Dombrowski SM, Desai SY, Marroni M, Cucullo L, Goodrich K, Bingaman W, Mayberg MR, Bengez L, Janigro D. Overexpression of multiple drug resistance genes in endothelial cells from patients with refractory epilepsy. Epilepsia 2001;42:1501-1506.

Ellerkmann RK, Remy S, Chen J, Sochivko D, Elger CE, Urban BW, Becker A, Beck H. Molecular and functional changes in voltage-dependent Na$^+$ channels following pilocarpine-induced status epilepticus in rat dentate granule cells. Neuroscience. 2003;119:323-333.

Hitiris N, Mohanraj R, Norrie J, Sills GJ, Brodie MJ. Predictors of pharmacoresistant epilepsy. Epilepsy Res 2007;75:192-196.

Kuo C-C, Lu L. Characterization of lamotrigine inhibition of Na$^+$ channels in rat hippocampal neurones. Br J Pharmacol 1997;121:1231-1238.

Kuo C-C. A common anticonvulsant binding site for phenytoin, carbamazepine, and lamotrigine in neuronal Na$^+$ channels. Mol Pharmacol 1998;54:712-721.

Leschziner GD, Andrew T, Pirmohamed M, Johnson MR. ABCB1 genotype and PGP expression, function and therapeutic drug response: a critical review and recommendations for future research. Pharmacogenomics J. 2007;7:154-179.

Leschziner GD, Jorgensen AL, Andrew T, Williamson PR, Marson AG, Coffey AJ, Middleditch C, Balding DJ, Rogers J, Bentley DR, Chadwick D, Johnson MR, Pirmohamed M. The association between polymorphisms in RLIP76 and drug response in epilepsy. Pharmacogenomics. 2007;8:1715-1722.

Löscher W, Potschka H. Drug resistance in brain diseases and the role of drug efflux transporters. Nat Rev Neurosci 2005;6:591-602.

Löscher W, Sills GJ. Drug resistance in epilepsy: Why is a simple explanation not enough? Epilepsia 2007;48:2370-2372.

MacDonald BK, Johnson AL, Goodridge DM, Cockerell OC, Sander JW, Shorvon SD. Factors predicting prognosis of epilepsy after presentation with seizures. Ann Neurol 2000;48:833-841.

Meldrum BS, Rogawski MA. Molecular targets for antiepileptic drug development, Neurotherapeutics 2007;4:18-61.

Remy S, Gabriel S, Urban BW, Dietrich D, Lehmann TN, Elger CE, Heinemann U, Beck H. A novel mechanism underlying drug resistance in chronic epilepsy. Ann Neurol 2003;53:469-479.

Rogawski MA. Does P-glycoprotein play a role in pharmacoresistance to antiepileptic drugs? Epilepsy and Behavior 2002;3: 493-495.

Rogawski MA. Progesterone, neurosteroids, and the hormonal basis of catamenial epilepsy, Ann Neurol 2003;53: 288-291.

Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs. Nat Rev Neurosci. 2004;5:553-564.

Rogawski MA, Taylor CP. Ion channels, In: Löscher W, Schmidt D: New horizons in the development of antiepileptic drugs: Innovative strategies. Epilepsy Res 2006;69:183-272.

Rogawski MA. Diverse mechanisms of antiepileptic drugs in the development pipeline. Epilepsy Res 2006;69:273-294.

Schmidt D, Löscher W. Drug resistance in epilepsy: putative neurobiologic and clinical mechanisms. Epilepsia 2005;46:858-877.

Shorvon S, Luciano AL. Prognosis of chronic and newly diagnosed epilepsy: revisiting temporal aspects. Curr Opin Neurol 2007;20:208-212.

Sillanpää M. Remission of seizures and predictors of intractability in long-term follow-up. Epilepsia 1993;34:930-936.

Sills GJ, Kwan P, Butler E, de Lange EC, van den Berg DJ, Brodie MJ. P-glycoprotein-mediated efflux of antiepileptic drugs: preliminary studies in mdr1a knockout mice. Epilepsy Behav 2002;3:427-432.

Soranzo N, Kelly L, Martinian L, Burley MW, Thom M, Sali A, Kroetz DL, Goldstein DB, Sisodiya SM. Lack of support for a role for RLIP76 (RALBP1) in response to treatment or predisposition to epilepsy. Epilepsia 2007;48:674-683.

Stafstrom CE. Persistent sodium current and its role in epilepsy. Epilepsy Curr 2007;7:15-22.

Tate SK, Depondt C, Sisodiya SM, Cavalleri GL, Schorge S, Soranzo N, Thom M, Sen A, Shorvon SD, Sander JW, Wood NW, Goldstein DB. Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. Proc Natl Acad Sci USA 2005;102:5507-5512.

Tate SK, Singh R, Hung CC, Tai JJ, Depondt C, Cavalleri GL, Sisodiya SM, Goldstein DB, Liou HH. A common polymorphism in the SCN1A gene associates with phenytoin serum levels at maintenance dose. Pharmacogenet Genomics 2006;16:721-726.

Tishler DM, Weinberg KI, Hinton DR, Barbaro N, Annett GM, Raffel C. MDR1 gene expression in brain of patients with medically intractable epilepsy. Epilepsia 1995;36:1-6.

van Vliet EA, van Schaik R, Edelbroek PM, Redeker S, Aronica E, Wadman WJ, Marchi N, Vezzani A, Gorter JA. Inhibition of the multidrug transporter P-glycoprotein improves seizure control in phenytoin-treated chronic epileptic rats. Epilepsia 2006;47:672-680.

Vreugdenhil M, Wadman WJ. Modulation of sodium currents in rat CA1 neurons by carbamazepine and valproate after kindling epileptogenesis. Epilepsia 1999;40:1512-1522.

Yang YC, Kuo CC. Inhibition of Na$^+$ current by imipramine and related compounds: different binding kinetics as an inactivation stabilizer and as an open channel blocker. Mol Pharmacol 2002;62:1228-1237.

Correspondence:
Michael A. Rogawski, M.D., Ph.D.
Department of Neurology
University of California, Davis
4860 Y Street, Suite 3700
Sacramento, California 95817
Telephone: 916-734-6275
Fax: 916-734-6526
E-mail: rogawski@ucdavis.edu