

## ANIMAL MODEL OF CORTICAL DYSPLASIA FOR SCREENING CANDIDATE AEDS

### Effects of Antiepileptic Drugs on Induced Epileptiform Activity in a Rat Model of Dysplasia

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Seizure activity associated with cortical dysplasia (CD) is often resistant to standard pharmacologic treatments. Although several animal models exhibit CD, virtually nothing is known about antiepileptic drug (AED) responses in these animals. Here we used rats exposed to methylazoxymethanol acetate (MAM) in utero, an animal model featuring nodular heterotopia, to investigate the effects of AEDs in the dysplastic brain. 4-Aminopyridine (AP; 100  $\mu$ M), a  $K^+$  channel blocker, was used to induce interictal epileptiform bursting in acute hippocampal slices from MAM-exposed and age-matched vehicle-injected control animals. Extracellular field recordings were used to monitor seizure activity in vitro. Five commonly used AEDs were tested: Phenobarbital (PB), 25–400  $\mu$ M; carbamazepine (CBZ), 25–200  $\mu$ M; valproate (VPA), 0.19–4 mM; ethosuximide (ESM), 0.5–8 mM; and lamotrigine (LTG), 49–390  $\mu$ M. 4-AP-induced bursting occurred with shorter latencies in slices from MAM-exposed rats in comparison with slices from controls, confirming the intrinsic hyperexcitability of dysplastic tissue. Each AED tested demonstrated significant burst suppression in control slices, but interictal epileptiform bursting in MAM-exposed slices was resistant to these treatments. Even at the highest concentrations, VPA, ESM, and LTG had no effect on burst amplitude in slices from MAM-exposed rats. Pharmacoresistance was further tested by measuring seizure latencies in awake, freely moving rats after kainate administration (15 mg/kg, i.p.) with and without pretreatment with VPA (400 mg/kg, i.p.). Pretreatment with VPA prolonged seizure latency in control rats, but had no effect in MAM-exposed animals. These results suggest MAM-exposed rats exhibit a dramatically reduced sensitivity to commonly prescribed AEDs.

### COMMENTARY

Animal models used for initial screening of compounds for anticonvulsant activity have been chosen, at least in part, to subserve rapid throughput. Early drug development using the maximal electroshock (MES) model and the pentylenetetrazol (PTZ) model for preclinical testing resulted in phenytoin (PHT) and ethosuximide (ESM), two classic and useful AEDs for the treatment of partial seizures with or without secondary generalization and primary generalized seizures of the absence type, respectively. The utility of these models was further exemplified by the development of carbamazepine (CBZ), and later, the broad spectrum of clinical activity discovered in valproic acid (VPA). During the 1990s, the limitations of these models became increasingly apparent. Gabapentin (GBP) was active in the PTZ model, but proved to be ineffective in human absence epilepsy. Conversely, lamotrigine (LTG), which was ineffective in the PTZ model, possessed antiabsence activity in humans. Hosford and Wang (1) showed subsequently that the homozygous lethargic mouse (lh/lh) model predicted the activity of several new agents against human absence seizures with excellent correlation. Since then, levetiracetam (LEV), which was ineffective in both the MES and PTZ models, emerged as an important new AED.

Cortical dysplasia (CD) is being recognized as an important cause of drug-resistant epilepsy. Recent years have seen the emergence of several animal models of CD, but the activity of common AEDs in these models has not been studied extensively. In the present article, Smyth et al. report on the activity of five commonly used AEDs on epileptiform activity in hippocampal slices obtained from rats exposed to methylazoxymethanol (MAM) in utero, which produces nodular heterotopia in these animals. Epileptiform activity was induced in the slice preparation by using a  $K^+$  channel blocker, 4-aminopyridine (4-AP). VPA also was tested against seizures induced in vivo by the administration of kainic acid (KA). In the slice preparations derived from MAM-treated animals, none of the AEDs was capable of suppressing 4-AP-induced epileptiform bursts. The latency to KA-induced seizure activity (stage V or VI) was prolonged by VPA in control animals but not in those exposed to MAM. The results parallel the dismal efficacy

of AEDs well known to clinicians in patients with seizures attributable to CDs.

One might wonder about the importance of an article with essentially negative results. I would posit that the results highlight the futility of the traditional screening methods in ever discovering a useful compound for certain types of epilepsy and underscore the need for new models for drug discovery. Clearly, many of the genetic models (lh/lh mouse, genetically absence epilepsy-prone rats from Strasbourg) have not been routinely used for initial screening because of limitations in the number of animals available, whereas the labor and costs associated with models like kindling limit their use in initial screening. Thus these models are often used in evaluating compounds that first survive MES and PTZ screens. The

experience with LEV suggests that we may reject potentially very useful compounds with that approach; thus much remains to be done in developing labor- and cost-efficient methods for screening that can also better select AEDs for the treatment of human epilepsies.

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## Reference

1. Hosford DA, Wang Y. Utility of the lethargic (lh/lh) mouse model of absence seizures in predicting the effects of lamotrigine, vigabatrin, tiagabine, gabapentin, and topiramate against human absence seizures. *Epilepsia* 1997;38:408–414.