

## DRUG RESISTANCE IN EPILEPSY: IS THE ROLE OF UNDERLYING PATHOLOGY RELATED TO MULTIDRUG RESISTANCE PROTEIN?

### Major Vault Protein, a Marker of Drug Resistance, Is Upregulated in Refractory Epilepsy

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**PURPOSE:** The molecular basis of drug resistance in epilepsy is being explored. Two proteins associated with drug resistance in cancer, P-glycoprotein and multidrug resistance-associated protein 1, are upregulated in human epileptogenic pathologies. Other proteins associated with resistance in cancer include major vault protein (MVP) and breast cancer resistance protein (BCRP). We hypothesized that these proteins also would be upregulated in human epileptogenic pathologies.

**METHODS:** Hippocampal sclerosis (HS), focal cortical dysplasia (FCD), and dysembryoplastic neuroepithelial tumor (DNT) were studied by using immunohistochemistry for MVP and BCRP. Nonepileptogenic control and histologically normal brain adjacent to epileptogenic tissue were used for comparison.

**RESULTS:** MVP and BCRP were expressed ubiquitously in brain capillary endothelium. Ectopic upregulation of MVP was seen in hilar neurons in HS, dysplastic neurons in FCD, and lesional neurons in DNT. Only in HS cases were rare extralesional neurons immunoreactive. Glial upregulation was not seen. No qualitative upregulation of BCRP was noted.

**CONCLUSIONS:** These results show that more than one resistance protein may be upregulated in a given epileptogenic pathology and may contribute to drug resistance. Determination of the types, amounts, and distribution of such proteins will be necessary for rational treatment for drug resistance in epilepsy.

spite eight newly marketed drugs for epilepsy in the past decade, only a small minority of refractory patients becomes seizure free. Among individuals with recent-onset epilepsy, more than one third declare themselves refractory to medical therapy (1). A number of predictors have been identified, including a large number of seizures before initiation of therapy, failure to respond to initial treatment, as well as certain underlying pathologies, such as hippocampal sclerosis, cortical dysplasia, or dual pathology of hippocampal sclerosis and another lesion (1–3).

Likely more than one mechanism underlies drug resistance in epilepsy (4). Recently an interest has been expressed in the potential role of multidrug resistance proteins that are thought to mediate multidrug resistance in cancer. Previous studies demonstrated increased expression of multidrug resistance gene-1 P-glycoprotein (*MDR1*) and multidrug resistance-associated protein 1 (*MRP1*) in tissue removed at surgery from patients with refractory epilepsy, including those with hippocampal sclerosis, focal cortical dysplasia, and dysembryoplastic neuroepithelial tumors predominantly located in astrocytes (5). In the current study, Sisodiya et al. investigated major vault protein, a constituent of vaults that are another cellular component associated with multidrug resistance. They found that major vault protein was upregulated in neurons in hippocampal sclerosis, focal cortical dysplasia, and dysembryoplastic neuroepithelial tumors. Major vault protein was not upregulated in normal neurons bordering the lesions or in normal neurons within the dysplasia.

This study suggests that multidrug resistance proteins may indeed play a major role in medically refractory epilepsy, as these proteins seem specifically upregulated in pathological processes known to be associated with antiepileptic drug (AED) resistance. However, to be more confident of the specificity and role of major vault protein upregulation in AED resistance, it should not be demonstrated in patients with medically responsive epilepsy. A direct relation between major vault protein upregulation and AED resistance would be more convincing if the upregulation were observed only in patients with refractory epilepsy. Because patients who have responded well to AEDs rarely present for epilepsy surgery (unless resection of a lesion is clinically indicated), it would be difficult to locate an adequate number of subjects for immunohistochemistry. Nevertheless, a better understanding of the role of transport proteins and

### COMMENTARY

**D**rug resistance has been a major problem in epilepsy therapy, fueling the search for more effective agents. Yet de-

their influence on specific AEDs may be crucial for progress in the medical treatment of refractory epilepsy. In particular, research efforts might target development of AEDs that are not influenced by multidrug resistance proteins or development of agents that can inhibit these proteins.

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