

THE ROLE OF DRUG-RESISTANCE PROTEINS IN MEDICALLY REFRACTORY EPILEPSY

Drug Resistance in Epilepsy: Expression of Drug-resistance Proteins in Common Causes of Refractory Epilepsy

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Epilepsy is resistant to drug treatment in about one third of cases, but the mechanisms underlying this drug resistance are not understood. In cancer, drug resistance has been studied extensively. Among the various resistance mechanisms, overexpression of drug-resistance proteins, such as multidrug resistance gene-1 P-glycoprotein (MDR1) and multidrug resistance-associated protein 1 (MRP1), has been shown to correlate with cellular resistance to anticancer drugs. Previous studies in human epilepsy have shown that MDR1 and MRP1 also may be overexpressed in brain tissue from patients with refractory epilepsy; expression has been shown in glia and neurons, which do not normally express these proteins. We examined expression of MDR1 and MRP1 in refractory epilepsy from three common causes, dysembryoplastic neuroepithelial tumors (DNTs; eight cases), focal cortical dysplasia (FCD; 14 cases), and hippocampal sclerosis (HS; eight cases). Expression was studied immunohistochemically in lesional tissue from therapeutic resections and compared with expression in histologically normal adjacent tissue. With the most sensitive antibodies, in all eight DNT cases, reactive astrocytes within tumor nodules expressed MDR1 and MRP1. In five of eight HS cases, reactive astrocytes within the gliotic hippocampus expressed MDR1 and MRP1. Of 14 cases of FCD, MDR1 and MRP1 expression was noted in reactive astrocytes in all cases. In five FCD cases, MRP1 expression also was noted in dysplastic neurons. In FCD and DNTs, accentuation of reactivity was noted around lesional vessels. Immunoreactivity was always more frequent and intense in lesional reactive astrocytes than in glial fibrillary acidic protein-positive reactive astrocytes in adjacent histologically nor-

mal tissue. MDR1 is able to transport some antiepileptic drugs (AEDs), and MRP1 also may do so. The overexpression of these drug-resistance proteins in tissue from patients with refractory epilepsy suggests one possible mechanism for drug resistance in patients with these pathologies. We propose that overexpressed resistance proteins reduce the interstitial concentration of AEDs in the vicinity of the epileptogenic pathology and thereby render the epilepsy caused by these pathologies resistant to treatment with AEDs.

P-Glycoprotein and Multidrug Resistance-associated Protein Are Involved in the Regulation of Extracellular Levels of the Major Antiepileptic Drug Carbamazepine in the Brain

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Despite considerable advances in the pharmacotherapy of epilepsy, about 30% of epilepsy patients are refractory to antiepileptic drugs (AEDs). In most cases, a patient who is resistant to one major AED also is refractory to other AEDs, although these drugs act by different mechanisms. The mechanisms that lead to drug resistance in epilepsy are not known. Recently, overexpression of multidrug transporters, such as P-glycoprotein (PGP) and multidrug resistance-associated protein (MRP), has been reported in surgically resected epileptogenic human brain tissue and suggested to contribute to the drug resistance of epilepsy. However, it is not known to what extent multidrug transporters such as PGP or MRP are involved in transport of AEDs. In the present study, we used in vivo microdialysis in rats to study whether the concentration of carbamazepine in the extracellular fluid of the cerebral cortex can be enhanced by inhibition of PGP or MRP, using the PGP inhibitor verapamil and the MRP inhibitor probenecid. Local perfusion with verapamil or probenecid

via the microdialysis probe increased the extracellular concentration of carbamazepine. The data indicate that both PGP and MRP participate in the regulation of extracellular brain concentrations of the major AED carbamazepine.

COMMENTARY

Antiepileptic drug (AED) resistance leading to the refractory epilepsy state has long been an area of intensive research. As reported in the last issue of *Epilepsy Currents*, new data indicate that patients may demonstrate drug resistance early in the course of epilepsy (1,2). This has, if anything, increased the research efforts aimed at discovering the basis of this phenomenon. One line of promising research, overexpression of multidrug transporters, is discussed in these two articles. These transporters are located at the blood–brain and blood–CSF barriers. Their role is to prevent lipophilic molecules from entering the brain. Many AEDs are thought to be substrates for these transporters, which may block access of these compounds to their site of action in the CNS, in the face of therapeutic serum levels. Tishler et al. (3) first reported 10-fold elevations of MDR-1, one of these transporter proteins, in the epileptic foci of drug-resistant epilepsy patients. MDR-1 is a *p*-glycoprotein found in astrocyte foot processes surrounding blood vessels. Another transporter that has been extensively studied is MRP-1 (multidrug resistance-associated protein). These transporters have been thought to play an important role in the development of resistance to anticancer treatments (4), but their role in multidrug-resistant epilepsy has been unclear. The elegant work reported in these two articles adds credence to the hypothesis that they may play a significant role in epilepsy. A few groups have identified elevations of these proteins in patients with pathologies commonly associated with drug refractoriness, such as tuberous sclerosis (5). Sisodiya et al. now report overexpression of both MRP1 and MDR1 in epileptic tissue surrounding dysembryoplastic neuroepithelial tumors (DNT), focal cortical dysplasia (FCD) and hippocampal sclerosis (HS), whereas adjacent nonepileptic tissue from the same patients did not show these elevations. Presence of focally increased transporter proteins could produce a situation in which relevant AEDs could enter normal brain, and thereby produce CNS side effects, but could be blocked from entering tissue surrounding the focus.

Although this investigation in human tissue is very important and relevant, it leaves several questions unanswered. For example, the immunohistochemical techniques used cannot determine the functional status of the transporters, nor can it be determined which AEDs might be substrates. For this reason, researchers have turned to animal models to study the ef-

fect of these multidrug resistance proteins (MRPs) on AEDs. Preliminary studies indicate that seizures provoked by kainic acid can upregulate expression of MRP (6,7). Potschka et al. now investigate the effect of MRP expression on AED transport. By using MDR-1 and MRP blockers (the common drugs verapamil and probenecid), they were able to increase the extracellular concentration of carbamazepine (CBZ) in rats. They found similar results for phenytoin (PHT), and it is likely that these proteins may affect transport of many other AEDs (8). One very intriguing finding was that there was a great deal of variability in the degree to which CBZ concentrations increased as a result of administering blocking agents. This might suggest genetic heterogeneity in the expression of MDR-1 and MRPs, even in the nonepileptic state.

These two experiments clearly imply that protein transporters may play a role in AED resistance. However, they suggest that both underlying genetic makeup as well as underlying pathological substrate may play a role in the expression of these transporters. Clearly, the degree to which each of these is important in a given patient would potentially influence therapeutic strategy. For example, administering a transporter blocker such as verapamil in the case of focal overexpression might just serve to increase side effects by increasing drug exposure in normal brain.

While these results are very interesting, there is a great deal more work to be done. The elegant work cited here must be duplicated in other laboratories. More AEDs must be tested to determine whether they are substrates for MRPs. More investigation is needed in patients with drug-resistant epilepsy.

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