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Transporters in Drug-Refractory Epilepsy: Clinical Significance

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Abstract

Drug resistance remains an unmet challenge in a variety of neurological disorders, but epilepsy is probably the refractory disease that has received most experimental, preclinical, and therapeutic attention. Although resective surgery continues to improve our ability to provide seizure relief, new discoveries have potential as alternative therapeutic approaches to multiple drug resistance. As discussed here, the field is replete with controversies and false starts, in particular as it concerns the existence of genetic predisposition to inadequate pharmacological seizure control.

Epileptic seizures are electrical events that produce a complex behavioral response ranging from absence to convulsions. Most epileptic patients respond well to one or more antiepileptic drugs (AEDs), but a small but significant (~20%) proportion of epileptics have or develop a poor pharmacological response. The term “drug resistance” implies the failure of a given pharmacological treatment. In analogy with drug resistance in oncology, certain forms of epilepsy do not respond to the available antiepileptic medications, thus becoming candidates for surgical intervention. As for every complex pathological condition, several disparate and often contrasting hypotheses have been formulated to explain the pathobiology of drug resistance in epilepsy:

1. The drug fails to reach the neuronal target (pharmacokinetic hypothesis). This includes the cerebrovascular overexpression of multidrug transporter proteins and the involvement of altered brain homeostasis (e.g., brain edema, blood–brain barrier (BBB) damage, and parenchymal extravasation of serum proteins).^{1,2}
2. The drug fails to act at the neuronal target (pharmacodynamic hypothesis³).
3. Seizure phenotype and history of seizures determine the “level of refractoriness” (the inherent disease severity hypothesis⁴).

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CONFLICT OF INTEREST

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In this mini-review, we focus primarily on the role of multidrug transporter (MDT) overexpression in drug-resistant epilepsy, but it is likely that multidrug resistance is the result of a multifaceted phenomenon ranging from drug pharmacodynamic and pharmacokinetic modifications to the underlying pathology and seizure history. Epidemiological studies have been performed to address the merit of these hypotheses. After a decade of studies, the role of MDTs is still controversial. What is the real impact of MDT overexpression in the epileptic brain? Is overexpression of MDTs exclusively associated with drug resistance, or do MDTs contribute to exaggerated seizure burden? Is it possible to diagnose drug resistance based on MDT polymorphisms?

In recent years, it has become evident that the epileptic brain has a tendency to overexpress a broad spectrum of MDTs. This was first shown for MDR1 (or P-glycoprotein, P-gp) but was then extended to the whole family of genes encoding transporters.⁵ Whereas the initial evidence demonstrated MDT overexpression at the BBB, glial and neuronal expression was reported shortly thereafter, raising the possibility of a neuroglial role for MDTs. Expression of MDR1 favors the least fit (a process termed pathobiosis⁶), promoting a process whereby malfunctioning cells are allowed to survive in an otherwise hostile environment; this phenomenon would in turn impede pruning of misguided neuronal connections or promote survival of defective glia. This results in a more robust seizure phenotype, hindering drug efficacy. According to this scenario, the transporter function of MDTs represents the iceberg tip of a broader pathological condition. An intriguing hypothesis is that altered cell cycle checkpoints and presence of MDT proteins link drug-resistant epilepsy to low-grade tumors.⁷

Another twist to the drug-transporter tale is the involvement of polymorphic forms of MDTs in defining seizure severity or AED refractoriness. The whole field of pharmacokinetic drug resistance has been the focus of renewed attention following the discovery of common polymorphisms for the *MDR1* (or *ABCB1*) gene. Recent genetic studies have suggested that the MDT protein levels are elevated in epileptics and that a specific polymorphic form predominates in epileptics affected by drug resistance.⁸ In particular, these studies suggested not only that MDR1 is responsible for drug ineffectiveness in these patients but that perhaps a more “potent” form of this transporter is present in these individuals. After a surprisingly short lag time, however, what appeared to be a probable and exploitable mechanism of AED resistance has resulted in another false start, as underscored by the lack of support for these initial findings. This study failed to be reproduced,⁹ and the notion that genetic variations among epileptics are responsible for refractoriness is not currently accepted. These results do not *per se* rule out that these variants are indeed involved in the process leading to refractoriness but instead highlight the immature state of “pharmacogenomics.” In light of the complex biology of chemotherapy resistance, these confounders are not surprising, because MDR1 expression represents only one of the multitudes of mechanisms that can lead to drug resistance. A positive association between MDR1 expression levels and drug-resistant epilepsy remains supported by experimental evidence. The manner in which this can be exploited to patients’ benefit remains elusive.

Because there is no question that the epileptic brain expresses abnormal levels of MDTs,² determining its significance is an intriguing question. What is the functional relevance of

MDT BBB overexpression? Can AED levels be manipulated by blocking MDTs?

Experimental evidence obtained using a rodent model of epilepsy suggests that MDR1 blockade increases brain drug levels and reduces seizure burden. Recent clinical trials have aimed to enroll patients for add-on therapy with MDT inhibitors (e.g., verapamil or probenecid). Preliminary data are not yet available, but the lessons learned from neuro-oncology suggest limited efficacy and possible side effects.

A bridge between MDT expression and pharmacodynamics has recently been provided.¹⁰ These authors have shown that when pooling the general population for MDR1 polymorphisms, an unexpected relationship between polymorphic variants and epilepsy becomes apparent. This implies that the multidrug-resistant phenotypes are due to exacerbated seizures in individuals bearing the MDR1 variant that was formerly believed to alter drug levels in the brain.

Another recognized caveat with an MDT-based mechanism of multidrug resistance is the uncertain interaction between AEDs and MDTs. Contradictory findings have been obtained by testing the AED transport *in vitro*. For example, there is no agreement as to which transporter transports which drug. In addition, the *in vitro* models used to screen drugs do not mimic the physiological condition of (epileptic) brain capillaries, leading to results that are not representative of the *in vivo* condition. The bases of drug resistance in epilepsy are found in the patient history and are perhaps related to pathological events such as traumatic brain injury, perinatal stress, and malformation of brain development. Most cases of drug-resistant seizures fall in the symptomatic category of epilepsies, in which the diagnosis of a precipitating event or pathology is possible. These clinical data are often not taken into account when considering or designing the next experimental model or *in vitro* experiment. Laboratory research is based on models of epilepsy that range from acute seizures (e.g., those caused by kainate toxicity) to chronic seizures (e.g., pilocarpine-induced status epilepticus). Animal models are often developed following a hypothesis-biased process rather than by taking into account the pathophysiology of the disease itself. A fundamental aspect that separates animal models from disease pathology is failure to recognize that (i) seizures occur in epileptics as well as in nonepileptics, (ii) the causes of seizures in epileptics (e.g., menses, sleep deprivation, fever) are different from the causes of acute “nonepileptic” seizures (e.g., alcohol withdrawal, cerebrovascular accidents, brain tumors), and (iii) models such as kainate toxicity or electroshock mimic acute symptomatic provoked seizures but not epilepsy. The best future course of action is to substantially alter the science to match the medicine, and in particular to follow epidemiological data rather than pursue mechanisms.

Finally, if surgery is—and will be for the foreseeable future—the “drug of choice” for multidrug resistance, greater scientific effort should be directed toward the improvement of imaging studies, resective techniques, mapping, and monitoring. If patients tend to become responsive to drugs following surgery, this would suggest that neurosurgical interventions treat drug resistance and not seizures. If this hypothesis proves valid, then we may well accept that multidrug-resistant epilepsy constitutes two diseases: one related to abnormal neuronal firing and the other to insufficient drug efficacy or levels. Conceivably, the failure

of current therapeutic advancements stems from our attempts to treat a poorly defined disease or, rather, a cluster of diseases with unknown components.

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Figure 1.

Schematic of the consequences of multidrug-resistance (MDR; P-glycoprotein) transporters in epileptic brain (right). Nonepileptic brain function is shown on the left. b.l., basal lamina; t.j., tight junctions between endothelial (Endo) cells. Note that according to this scenario, only endothelial MDR expression affects drug penetration, whereas parenchymal expression is related to the survival of otherwise pathological neurons and glia. Also note that the tight junctions are impaired in epileptic brain. The question mark refers to yet-unknown pathways of drug passage when a leaky blood–brain barrier is present.¹

Table 1

Proposed mechanisms of refractoriness to antiepileptic drugs

Mechanism	Evidence for	Evidence against
Pharmacokinetic	MDR protein is overexpressed in epileptic brain	Not all AEDs are MDT substrates. Different results are obtained from different animal or cellular models
Pharmacodynamic	Sodium channel mutations reduce AED efficacy. Cognate target is not present (e.g., SCN1A)	<i>In vitro</i> neuronal response to AED is not affected
Homeostatic	Animal studies show reduced levels in edematous regions	Lack of solid imaging data on edema in epileptic brain
Seizure severity/susceptibility genes	Animal models of seizures; epidemiology	Lack of reproducibility in human studies

AED, antiepileptic drug; MDT, multidrug transporter.