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Minireview

Potential role of multidrug resistant proteins in refractory epilepsy and antiepileptic drugs interactions

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Abstract

Epilepsy is a common neurological disorder. About one-third of epilepsy patients have a multidrug resistance (MDR) phenotype and develop refractory epilepsy (RE). Changes in the properties of the antiepileptic drugs (AEDs) targets resulting in reduced drug sensitivity, can't explain the MDR phenotype. This particular refractoriness is now attributed to overexpression of multidrug transporters in brain, leading to impaired access of AEDs to CNS targets, and it was documented in both human as well as in experimental models of RE. Single nucleotide polymorphism (SNP) identified in the *MDR1-ABCB1* gene (*C3435T/CC-genotype*) is associated with increased intestinal expression of P-glycoprotein (P-gp) that affects levels of AEDs in plasma. The functional studies of P-gp using P-gp inhibitors could show the still unclear clinical impact of *ABCB1* polymorphisms on AEDs resistance. Some drug-drug interactions previously believed to be cytochrome P450 (CYP) mediated are now also considered to be due to the modulation of multidrug-transporters. Because in certain cases pharmacoresistance can be overcome by add-on therapy, co-administered P-gp inhibitors could contribute to the effectiveness of AEDs treatment in RE. And in this regard, perhaps we can postulate to P-gp as a new clinical therapeutic target in multidrug-refractory epilepsy.

Keywords: antiepileptic drugs; epileptogenesis; nimodipine; P-glycoprotein; refractory epilepsy.

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Introduction

Epilepsy is a very common neurological disorder, perhaps being the most prevalent chronic neurological disorder affecting at least 50 million people worldwide. Epilepsy is the tendency to have recurrent seizures unprovoked by systemic or acute neurologic insults, and AEDs are those which decrease the frequency and/or severity of seizures in epileptic patients. Although to date there is no convincing evidence that AEDs "cure" the epileptic syndromes, the therapeutic goal will be maximizing seizure control while minimizing adverse drug effects, thus improving the patient's quality of life. Many epileptic patients (approx. 70%) have well-controlled seizures with currently available AEDs and patients whose seizures have been completely controlled for two or more years could be successfully withdrawn from AEDs.

Unfortunately, seizures can persist in a considerable proportion of patients (approx. 30%) who do not respond to any of two to three first line AEDs and these patients will develop refractory epilepsy (RE) (1). Irrespective to a poor compliance or inappropriate selection of first-line antiepileptic drugs, certain clinical features observed in some epileptic syndromes appear to correlate with pharmacoresistant phenotype. Interestingly, the optimal doses of AEDs may differ four-fold among individuals (2), and treatment with optimal doses of AEDs in individual patients could have unpredictable efficacy, ranging from adverse drug reactions to complete refractoriness (3). Moreover, unexpected persistent low levels of AEDs in plasma, even receiving higher AEDs doses have also been described in several cases of RE (4, 5).

Multiple drug resistance is characterized by insensitivity to a broad spectrum of drugs that presumably act on different receptors and by different mechanisms.

Why a subgroup of patients repeatedly fails to control the seizures with one AED after another?

Two concepts have been put forward to explain the development of pharmacoresistance in RE patients. The "*target hypothesis"* holds that epilepsy-related changes in the properties of the drug targets themselves results in reduced AEDs sensitivity.

These pharmacodynamic changes cannot fully explain the treatment failure after several drugs aimed at various therapeutic targets, are simultaneously administered and patients remains without crisis control. The other hypothesis

suggests that an increase of functional expression of multidrug transporters in the brain produces pharmacokinetics changes that modify the access of AEDs to CNS targets (1). Because in the clinical setting it is rather difficult to distinguish between the contributions of a potential pharmacodynamic interaction in the presence of pharmacokinetic interactions, perhaps both mechanisms may be acting simultaneously.

There is no published evidence to suggest that even newer AEDs have resulted in better treatment outcomes. It is reasonable to postulate that a common powerful mechanism, may limit the effectiveness of all different available AEDs irrespective on their mechanisms of action or their chemical properties. Several drug-transporters are normally expressed in the apical membrane of capillary endothelial cells that form the blood-brain barrier (BBB), but in responders patients, this normal expression does not limits the access of AEDs to the CNS. Consequently, functional overexpression of these transporters at BBB and/or brain parenchyma cells (neurons, astroglial cells) should be observed in drug resistant epileptic patients according with the mentioned "transporter hypothesis".

The first clinical evidences of this hypothesis were initially described for P-glycoprotein (P-gp) encoded by *MDR-1/ABCB1 gene*, showing P-gp overexpression in specimens from epileptogenic lesions of patients with different RE syndromes surgically treated. Additionally, multidrug-resistance-associated proteins (MRPs), breast cancer resistant protein (BCRP) and mayor vault protein (MVP), were also reported to be overexpressed in both clinical as well as experimental pharmacoresistant epilepsy (4–10).

The interindividual differences of epilepsy treatment and AEDs pharmacokinetics

Increased transporter expression could be due to the epileptic process itself or secondary to the occurrence of repetitive seizures. Because prognosis varies considerably among the different types of epilepsy as well as the treatment outcome may vary even between patients with seemingly the same epilepsy syndrome (3), genetic polymorphisms in these transporters could account for their increased expression and/or functional activity and perhaps explain the interindividual differences observed during disease evolution and clinical endpoints in pharmacologic epilepsy treatment. These genetic variations could be linked with changes on pharmacokinetic or pharmacodynamic of AEDs.

Recent advances in molecular medicine have led to the perspective that individual differences in responsiveness to drugs could be the result of a complex combination of genetic and environmental factors. The well-documented genetic polymorphisms in drug metabolism have contributed significantly to the understanding of the interindividual variability in dose concentration relationships and AEDs response. A number of important human drug transporters have been identified to be expressed at the apical or basal side of the epithelial cells in various tissues. These transporters belong to ABC (ATP-binding cassette) superfamily including transporters of cellular efflux of endogenous and exogenous substrates, and they have pharmacogenetic relevance. Most AEDs are substrates of these transporters and consequently, the potential impact of their functional expression could have clinical utility in the prognosis on specific AED treatments.

Because most AEDs are administered orally, variations on genes related with drug absorption (transport and metabolism) will govern drug plasmatic levels as well as drug distribution and their access to the CNS. Enterocytes and hepatocytes express the major AEDs-metabolizing enzymes (CYP family), and multidrug-transporters (P-gp, MRPs, BCRP) playing a crucial role by limiting drug absorption as well as regulating their metabolization and excretion ratio (11).

Additionally, plasma proteins such as albumin and α1-acid glycoprotein may regulate the interaction level of free drug with their targets, in equilibrium with systems of drug metabolism and excretion. However, studies on the relationship between plasma protein polymorphisms and clinical endpoints of therapeutic responsiveness related with AEDs and refractoriness have not been poorly reported.

The debate on genetic variants and AEDs treatment success

Most AEDs are mainly metabolized in the liver by mechanisms of hydroxylation (phase I) and/or conjugation (phase II). Phase I reactions involve the cytochrome P450 (CYP) family, and although 18 family members have been identified, the principle CYP enzymes involved in AEDs metabolism include CYP2C9, CYP2C19 and CYP3A4. Hepatic CYP enzymes can be either induced or inhibited by several AEDs resulting in changes of the pharmacokinetic properties of different medications. Enzyme inducers decrease the serum concentrations of other drugs and enzyme inhibitors have the opposite effect, and inhibitors will decrease the clearance and will increase the steady-state concentrations of other substrates. There is a significant overlap between ABCB1 and CYP3A4 substrates and inhibitors (as well as inducers). Because some drug interactions, previously believed to be cytochrome P450 (CYP) mediated, are now also considered to be due to the modulation of transport proteins, so it is often difficult to distinguish particularly between inhibition of CYP-system and the inhibition of transporters (Table 1) (12).

As mentioned for enterocytes, systems of metabolism and transport efflux of drugs are expressed in liver and in concert all these mechanisms can also modify the rate of drug degradation and excretion, affecting the plasmatic levels of AEDs. Although ultrarapid drug metabolism of drugs which are resistant to pharmacotherapy affecting plasmatic levels was reported many years ago (13), the overexpression of several ABC-transporters, particularly P-glycoprotein (*MDR-1/ABCB1 gene*) has been recognized to play a central role in the pharmacoresistant phenotype in epilepsy by limiting the drug efficacy as well as the plasmatic levels of AEDs in individualized cases (1, 8).

A single nucleotide polymorphism, (SNP) at the position *C3435T* in exon 26 of the *MDR1 gene*, is associated with differential intestinal expression of P-gp, where the homozygous

Table 1 AEDs as inducers or inhibitors of metabolic drug enzymes and as substrates of multidrug-resistant proteins.

AED	Induces		Inhibits		Metabolized by		ABC-transporter
	CYP	UGT	CYP	UGT	CYP	UGT	Substrate
Carbamazepine	2C9; 3A families	+	–	–	1A2; 2C8; 2C9; 3A4	No	P-gp; MRP2
Ethosuximide	No	No	No	No	?	?	?
Felbamate							P-gp
Gabapentin	No	No	No	No	No	No	P-gp
Lamotrigine	No	Yes	No	No	No	Yes	P-gp
Levetiracetam	No	No	No	No	No	No	?
Oxcarbazepine	3A4/5	Yes	2C19	Weak	No	Yes	?
Phenobarbital	2C9; 3A families	Yes	Yes	No	2C9/2C19	No	P-gp
Phenytoin	2C9; 3A families	Yes	Yes	No	2C9/2C19	No	P-gp; MRP-2
Tiagabine	No	No	No	No	3A4	No	?
Topiramate	No	No	2C19	No	–	–	P-gp
Valproate	No	No	2C9	Yes	2C9/2C19	Yes	MRP
Zonisamide	No	No	No	No	3A4	Yes	?

Modified from Patsalos et al., 2002 (12).

T-allele (*T3435T* or *TT* genotype) is associated with more than two-fold lower MDR-1 expression levels compared with samples from subjects homozygous for C-allele (*C3435C* or *CC* genotype), and heterozygous individuals display an intermediate phenotype (*T3435C* or *CT* genotype) (14). As consequences, lower plasmatic concentrations of digoxin (a specific P-gp substrate) after oral administration was observed in subjects carrying *CC* genotype compared with those with *TT* genotype, indicating that *CC* genotype have an increased intestinal P-gp expression and activity affecting digoxin intestinal absorption and plasmatic levels (15, 16). In this regards, correlation between intestinal expression levels and genetics of *CYP3A4, CYP2C9/19, MDR1* and *MRP2*, with dose requirement and plasma levels of carbamazepine and phenytoin evaluated in 44 epileptic patients, indicated that differences in intestinal MDR1 and MRP2 expression may influence carbamazepine and phenytoin disposition and may account for interindividual pharmacokinetic variability (17).

In an opposite way, an ethnic inverse difference was described by Sakaeda et al. who demonstrated that the serum concentration of digoxin was lower in the subjects harboring *TT* genotype (18) as well as higher duodenal absorption rates of digoxin for *CC* alleles (19). Consistent with these observations there are results from another Japanese study showing an association between *C3435T* and low intestinal expression of cytochrome P450 (CYP3A4), which, like *ABCB1 gene*, is located at chromosome 7q21 (20). Interestingly, it was also demonstrated that the inductions of CYP3A4 is associated with MDR-1 induction (21).

The discovery of genetic polymorphisms in drug metabolism has contributed significantly to the understanding of interindividual variability, both in dose concentration relationships and in drug response. The predictive value of MDR1, CYP2C9, and CYP2C19 polymorphisms as markers for phenytoin plasma levels has also been documented (22). In drug-resistant epilepsy, a study of *MDR1-C3435T* gene polymorphism showed that RE patients were more likely to have the CC genotype at ABCB1 3435, than the TT genotype, when compared to drug responsive epilepsy patients (23).

Nevertheless, a recent study of 400 epileptic patients failed to corroborate the association between these polymorphisms with RE phenotype (24).

To date, more than 20 publications that include almost 4000 epileptic patients, show controversial results and the relation between the MDR1/ABCB1 polymorphisms with pharmacoresistance in epilepsy are still unclear. Few of these studies have documented a positive association, whereas the other was unable to identify such association. These discrepancies could be explained by many factors, including sample size, sample homogeneity, sample bias, and diagnosis of the epilepsy syndromes and pharmacoresistance definitions (25). In a reduced group of patients with refractory epilepsy, the impact of polymorphisms *3435C>T* and *2677G>T* in the *ABCB1* gene on the ABCB1 mRNA expression and P-gp content was examined in human brain tissue from epileptogenic foci, and the authors conclude that they cannot exclude an association of ABCB1 variants on P-gp function, but their results suggest that brain ABCB1 mRNA and protein expression is not substantially influenced by major ABCB1 genetic variants thus explaining in part results from case-control studies obtaining lack of association of ABCB1 polymorphisms to the risk of refractory epilepsy (26).

A more complete study of the clinical impact of pharmacogenetics on the treatment of epilepsy, reviews the published works with particular emphasis on pharmacogenetic alterations that may affect efficacy, tolerability, and safety of AEDs, including variation in genes encoding drug target (*SCN1A*), drug transport (*ABCB1*), drug metabolizing (*CYP2C9, CYP2C19*), and human leucocyte (*HLA*) antigens. This study, suggest that the effect of a particular polymorphism (e.g., *ABCB1 3435C>T*) associated to prognosis in RE, may have little clinical relevance and may be misleading, because it may act in concert with other polymorphisms. However, postulate that one potential strategy to determine the clinical impact of ABCB1 polymorphisms on AED resistance in patients with epilepsy are clinical studies with P-gp inhibitors (9).

Individuals with *3435C/C* genotype have significantly higher activity of rhodamine efflux and higher ABCB1

expression in blood cells, as compared with those with *3435T/T* genotype (27). The use of inhibitors of ABCB1 transporter function could help in the treatment to patients with RE, and it can be monitored by a increased rhodamine-123 (Rho-123) accumulation in CD56+ T cells, perhaps in concordance with modification in the AEDs pharmacokinetic parameters and better control of seizures frequency.

Because the genetic debate still remains inconclusive, we believe that more sensitive functional studies, perhaps allow knowing the P-gp activity (or other transporters), closed related to therapeutics and clinical follow-up of epileptic patients, and offer a better method to the early identification of responders than no-responders patients.

AEDs interactions and inhibition of P-glycoprotein

A drug-drug interaction (DDI) occurs when one drug alters the effectiveness or toxicity of another and clinically significant drug interactions with potential harm to the patient may result from changes in pharmaceutical, pharmacokinetic, or pharmacodynamic properties. DDI based on pharmacokinetics or "what the body does to the drug", must be distinguished from those based on pharmacodynamics or "what the drug does to the body". DDI involving AEDs can cause serious morbidity and mortality if not anticipated and managed appropriately. For instance, an unexpected loss of seizure control or development of toxicity during AED therapy may accompany the addition or removal of a concurrently administered drug, and prevention of AED interactions is best achieved by avoiding unnecessary polytherapy.

Additionally, virtually all epilepsy patients will receive, at some time in their lives, other medications for the management of associated conditions. In these situations, clinically important DDI may occur. Then, which are the mechanisms of AEDs interaction? Even though some interactions at the pharmacodynamic level were documented, the main mechanism for AEDs interaction falls at the pharmacokinetic level. The most important pharmacokinetic parameters altered by AEDs administration are the rate of absorption, the rate of breakdown of a drug or metabolite, although the rate of CNS penetration should be also evaluated. For instance, carbamazepine, phenytoin, phenobarbital and primidone induce many cytochrome P450 (CYP) and glucuronyl transferase (GT) enzymes, and can reduce drastically the serum concentration of most other concurrently administered AEDs, most notably valproic acid (VA), that can be reduced on average by 50%–75% in patients comedicated with enzyme inducers. Inversely, VA will induces an already maximal inhibition of the metabolism of lamotrigine at dosages of valproate around 500 mg/day, resulting in near of two-fold increase in serum lamotrigine levels, with clinical consequences as skin rashes. Similarly, AV increases the plasmatic levels of ethosuximide and felbamate. Carbamazepine serum levels decrease by 17% after add-on therapy with VA, and additionally, VA displaces phenytoin (PHT) from its binding to plasma proteins and drastically decreases PHT plasmatic levels (11).

Therapeutic drug monitoring has been invaluable in identifying causes for variability in AED levels, which include genetic profile, age, pregnancy, concomitant disease, and drug-drug interactions. AEDs concentration in serum usually correlates with the concentration at the site of action (brain), however, drug concentration in serum fluctuates considerably during a dosing interval for those AEDs that are absorbed and eliminated rapidly.

The kinetics of AEDs penetration in the brain can be described by the extent and time to reach brain equilibrium depending from the ratio of free brain concentration to free plasma concentration at steady state. In spite of several documents being available, that are related with metabolic DDI issues and how to avoid them, unexpected DDI may occur and one factor may involve DDI mediated by drug transporters, particularly P-gp at the BBB. It is clear that drug interaction mediated by P-gp may have a great impact on drug disposition particularly regarding the brain.

The frequency of possible drug interactions increases with the number of concomitantly administered drugs, and these interactions can lead to serious adverse events resulting in harm to the patients.

However, it was observed that some patients with difficult-to-treat epilepsy had benefit from combination therapy with two or more AEDs and the reason for this particular therapeutic behavior has not been totally understood yet. According with these observations, the knowledge on DDI properties of selected drugs could help to avoid the pharmacoresistance mediated by functional overexpression of drug transporters. So, an inhibitory interaction of several AEDs with P-gp in vitro at concentrations exceeding therapeutic plasma concentrations have been described, suggesting that modulation of P-gp is not a major determinant of AED action in monotherapy. Interestingly, certain interactions could have a favorable impact, as has been shown for a series of add-on therapies, which are often more effective than monotherapies at similar plasma concentrations. So, it is possible that additive or even synergistic inhibition of transport may occur when several AEDs (or other therapeutic drugs) that compete for P-gp binding sites are given concomitantly (28).

In this regard, calcium channel blockers such as verapamil, diltiazem, nicardipine, niludipine, and nimodipine are well know high affinity substrates of P-gp and other ABC-transporters, and they competitively inhibit the efflux of other drug-substrates in mdr-1 positive cells, including AEDs. In this sense, our group has studied several pediatric refractory epilepsy cases with persistent sub-therapeutic AEDs blood levels. Nimodipine administration, together with AEDs, resulted in notable improvement of both medical condition and blood levels of AEDs. These results encouraged the inclusion of nimodipine in AED protocols for two other patients with refractory epilepsy. In both, additional administration of nimodipine improved the plasmatic levels of AEDs and stopped the occurrence of seizures avoiding the surgical treatment (29).

Similarly, Iannetti et al. (30) recently described an 11-year-old boy who developed status epilepticus, after a prolonged right-side simple partial motor seizure, which was unresponsive to long-term aggressive treatment with several AEDs. Control of convulsive seizures was achieved at a plasma valproic acid

level of 108 μg/mL, but electrical status epilepticus persisted, and the child remained comatose. On day 37, a treatment with verapamil (a calcium L-channel blocker and a known P-gp inhibitor) was started and 1.5 h after the initiation of the infusion, the patient regained consciousness and was able to breathe spontaneously, also the electrical status, promptly disappeared.

As mentioned above, it was observed in clinical RE cases that drug transporters could be overexpressed only at the epileptogenic brain areas. Therefore, medications may be unable to penetrate and stay within the parts of the brain that need them most. This may mean that the amount of drug is actually lower in the parts of the brain that cause seizures, and higher in the rest of the brain, which may be why patients may still feel side-effects when seizures are still occurring. More recently, a method was developed using the P-gp substrate R-[^{11}C]verapamil and positron emission tomography (PET) to test for differences in P-gp activity between epileptogenic and non-epileptogenic brain regions of patients with drug-resistant unilateral temporal lobe epilepsy. This study suggest that in future clinical trials with P-gp modulators, PET scans using R-[^{11}C]verapamil might be useful to identify patients with pronounced cerebral P-gp activity, which would most likely benefit from P-gp modulation (31).

Finally, an alternative mechanism to the classic pumping function of P-gp was observed in cells expressing MDR-1 gene. These cells exhibit significantly low membrane potential ($\Delta\Psi 0$=–10 to –20 mV) compared to the physiological potential ($\Delta\psi 0$ of –60 mV), leading to reduced (approx. 30%) binding of the drug (32). In neurons, these P-gp dependent potential membrane alterations ($\Delta\psi 0$), not only could contribute to develop the refractory phenotype, but also, in the intrinsic mechanisms of the epileptogenicity. In agreement with these concepts, a preliminary collaborative study showed the first evidence that repetitive seizures induce high neuronal P-gp overexpression associated with refractoriness and a concomitant progressive enrollment of hippocampal cells with depolarized membrane. Both refractoriness and depolarization were reversed after nimodipine administration. Irrespective to the well known drug transport property, neuronal P-gp overexpression, induced by many different causes, could be an additional mechanism for depolarization membrane that increase the risk for new seizures and so playing a role in the epileptogenesis (33) (Figure 1).

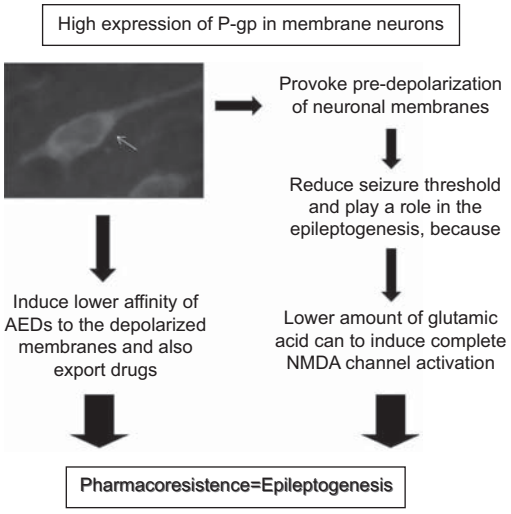

Figure 1 Potential dual role of P-gp in pharmacoresistance and epileptogenesis.

Future perspectives

Once we have elucidated the pharmacoresistance mechanisms to AEDs, this knowledge may become increasingly important both in drug development as well as clinically. Information on specific resistance mechanisms might also be used to guide potential treatment with drug transporter inhibitors in conjunction with AEDs. Additionally, if genetic polymorphisms in either transporter or AEDs-targets, genes can be identified and the probable mechanisms of drug resistance are also identified, it would influence on an individualized therapy, and perhaps increase the chances of its success (1).

According with concepts, several reports indicates that inhibition of the multidrug transporter P-gp significantly improves the anticonvulsive action of AEDs on experimental RE models (34, 35). Furthermore, a series of recent studies suggested several interesting targets, including the N-methyl-d-aspartate (NMDA) receptor, inflammatory enzyme cyclooxygenase-2, and the prostaglandin E2 EP1 receptor. Experimentally, it was demonstrated that targeting these factors P-glycoprotein expression can be controlled, improving AEDs brain penetration and helping to overcome the pharmacoresistance. All this information indicates that both the control of expression as well as functional inhibition of P-gp, can help to control seizures in RE. Perhaps, several add-on therapies will impact not only in the efflux properties of P-gp, but also in their depolarization effects. In this context current literature suggests that P-gp could be a new therapeutic target of drug-refractory epilepsy in the clinical practice (37–39).

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