How to Explain Multidrug Resistance in Epilepsy?

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Despite advancements in antiepileptic therapy, about one third of people with epilepsy will remain intractable to medication. The initial response to antiepileptic drug therapy is highly predictive of long-term outcome. However, the mechanisms of medical intractability of epilepsy are only incompletely understood. Current interest is focused on two hypotheses: overexpression of drug efflux transporters and alterations in drug targets in the brain, with the most relevant causative mechanism(s) still to be elucidated.

Despite significant advances in the therapy of epilepsy over recent decades, about one third of patients with epilepsy are only poorly controlled or their seizures are refractory to drug treatment (1,2). Patients with intractable epilepsy may have a progressive disorder that is medically, physically, and socially disabling (2). The initial response to antiepileptic drug (AED) therapy is highly predictive of long-term outcome (3). Most patients with refractory epilepsy will undergo multiple drug trials, most often without any noteworthy reduction in seizure frequency (3,4). A growing consensus agrees that failure of two AEDs places a patient in a category in which it becomes highly unlikely that further AEDs will successfully control the seizures, even when AEDs with different mechanisms of action are used (3,4). The mechanisms underlying this multidrug resistance in epilepsy are not well understood; however, a number of hypotheses exist and are critically discussed in this review.

Most clinical and experimental studies on multidrug resistance in epilepsy involve temporal lobe epilepsy (TLE), which is the most common and difficult-to-treat type of epilepsy in adults (5,6). Different scenarios or patterns of multidrug resistance exist in this and other types of epilepsy. In many patients with medically intractable epilepsy, epilepsy is refractory from the onset, suggesting that intrinsic (constitutive) factors are involved in intractability (7). However, in other patients, drug resistance may arise during the course of epilepsy after an initially positive response, suggesting that epilepsy-related, acquired changes affecting AED efficacy or progression of the disease are involved in intractability (7). Thus, any hypothesis of multidrug resistance has to deal with these and possibly other patterns in the occurrence and course of intractability in epilepsy. The fact that a minority of patients refractory to currently used drugs may become seizure free with new AEDs (8) seems to indicate that no absolute intractability. Thus, medically intractable seizures may become tractable, once we understand more about the mechanisms underlying intractability and how to prevent or reverse this state.

A number of clinical aspects appear to contribute to the biologic basis of refractory epilepsy, including an identified symptomatic etiology, early age at seizure onset, the type of epileptic syndrome and seizures, structural brain abnormalities or lesions (e.g., hippocampal sclerosis or cortical dysplasia), high number or frequency of seizures before onset of treatment, the persistence of seizures with treatment, and abnormal electroencephalographic findings (1,2,55). However, the prognostic value of most of these factors is rather limited, and none of these factors alone can explain multidrug resistance. For instance, although hippocampal sclerosis, which is considered a hallmark of mesial TLE, is the most common structural lesion associated with multidrug resistance, not all patients with hippocampal sclerosis are refractory to AEDs (5). Indeed, response to AEDs in newly diagnosed patients with hippocampal sclerosis is much better than response in difficult-to-control patients with TLE and hippocampal sclerosis who are referred to tertiary care centers, suggesting that the high rate of AED failure in such patients may reflect, in part, the overrepresentation of medically refractory patients in these centers (5).

Apart from these clinical aspects that potentially contribute to refractory epilepsy, currently two major hypotheses may explain medical refractoriness of seizures: the multidrug-transporter hypothesis and the drug-target hypothesis. These hypotheses, which are both plausible and based on a reasonable body of evidence, are discussed in more detail in the following sections.

Multidrug-transporter Hypothesis

Background Information

Multidrug resistance not only occurs in epilepsy but also has been acknowledged for many years as a major obstacle in therapy

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of cancer, rheumatic arthritis, bacterial infections, and several other diseases (9). Multidrug resistance is typically characterized by resistance to a broad range of structurally and functionally unrelated agents, suggesting the involvement of nonspecific mechanisms of resistance that affect diverse drugs, irrespective of their mechanisms of action. Studies on the mechanisms of multidrug resistance were initiated by the 1973 discovery by Keld Dano of the active outward transport of the chemotherapeutic agent daunomycin in drug-resistant tumor cells that had been selected in daunomycin, but were cross resistant to various other chemotherapeutic agents, such as doxorubicin and the *Vinca* alkaloids (10). Shortly thereafter, Victor Ling and colleagues correlated overexpression of a 170-kDa protein, termed P-glycoprotein (P-gp), with reduced drug accumulation and multidrug resistance in tumor cells (11). The gene encoding P-gp was cloned and named the *multidrug resistance-1* (*MDR1*) gene; expression of this gene was found in a variety of cancers, resulting in increased efflux of chemotherapeutics from cancer cells. The potential relevance of this finding for clinical oncology was further substantiated by the observation that verapamil was able to overcome this MDR1 phenotype in cancer cells by enhancing cytotoxicity of chemotherapeutic agents (12).

Subsequently, it was recognized that several compounds already in clinical use were able to inhibit P-gp, leading to the first clinical trials aimed at inhibiting P-gp–mediated drug efflux and, thereby, reversing clinical drug resistance in cancer patients (13). In addition to verapamil, these "first-generation" P-gp inhibitors include nifedipine, quinidine, amiodarone, nicardapine, quinine, tamoxifen, and cyclosporin A (13,14). As a result of a lack of selectivity and efficacy of these P-gp inhibitors and pharmacokinetic interactions, trials using such agents failed to prove convincingly the importance of P-gp inhibition in oncology (13). Because drug resistance remains one of the primary causes of suboptimal outcomes in cancer therapy, more selective, highly potent and nontoxic P-gp inhibitors were developed over recent years, including second-generation compounds, such as PSC-833 (valspodar), GF120918 (elacridar), VX-710 (biricodar), and dexverapamil, and third-generation compounds, including OC 144-093 (ONT-093), LY335979 (zosuquidar), XR9576 (tariquidar), R101933 (laniquidar), and GF120918 (14). Whereas second-generation agents have better tolerability but are still confounded by unpredictable pharmacokinetic interactions and interactions with other transporter proteins, third-generation inhibitors have high potency and specificity for P-gp (14). Several randomized trials have shown statistically significant benefits with the use of a P-gp inhibitor in combination with chemotherapy (15). As is discussed, such selective and nontoxic P-gp inhibitors also may be used to enhance the penetration of drugs, including AEDs, through the blood–brain barrier (BBB) (9).

Apart from P-gp, various other multidrug efflux transporters have been identified in multidrug-resistant cancer cells over recent years, including the multidrug resistance proteins (MRPs) and breast cancer resistance protein (BCRP) (9,16). All these transporters are members of the adenosine triphosphate (ATP)-binding cassette (ABC) transporter superfamily that regulates the trafficking of drugs, peptides, ions, and xenobiotics across cell membrane barriers (16). Three-dimensional modeling of human MDR1/P-gp indicates that these glycoproteins function as efficient ATP-dependent gatekeepers that scan the plasma membrane and its inner leaflet to flip lipophilic substrates to the outer membrane leaflet (17). ABC transporters such as P-gp, MRPs, and BCRP not only are expressed by cancer cells but also are located in the cell membrane of many normal tissues where they can extrude a variety of structurally diverse drugs, drug conjugates and metabolites, and other compounds from the cell, thus protecting the cell from cytotoxic concentrations of such agents (16). In the brain, P-gp, several MRPs, and BCRP are located in the apical (luminal) membrane of endothelial cells that form the BBB and combine to reduce the brain penetration and increase the brain extrusion of many drugs (9,18,19). Several major AEDs seem to be substrates for P-gp or MRPs, so that overexpression of such transporters at the BBB is likely to decrease brain concentrations of these drugs (9,20).

Clinical and Experimental Data Supporting the Multidrug-transporter Hypothesis

A markedly enhanced expression of *MDR1* and P-gp in BBB endothelial cells of epileptogenic brain tissue resected from patients with intractable epilepsy was first reported by Tishler et al. (21). Since then, various other reports have demonstrated overexpression of *MDR1* or P-gp in epileptogenic brain tissue of patients with different types of multidrug-resistant epilepsy, leading to the multidrug-transporter hypothesis of medically intractable epilepsy (9,20,22–24). Furthermore, several members of the MRP transporter family, including MRP1 and MRP2, were found to be overexpressed in such tissue. The overexpression of P-gp and MRPs was detected in BBB endothelial cells and astroglia, which normally do not express these transporters to any significant extent (9,20,22–24). Glial endfeet covering the blood vessels contribute to BBB function, so that overexpression of multidrug transporters in perivascular astroglia may represent a second barrier for AED penetration into the brain (22).

Similar to the findings in patients with multidrug-resistant epilepsy, overexpression of P-gp and MRPs in BBB endothelial cells and astroglia was determined in rodent models of TLE (9,20). In a mouse model of TLE, decreased brain concentrations of phenytoin (PHT) were found at the time of maximal

expression of P-gp, substantiating that enhanced expression of this efflux transporter is associated with decreased brain penetration of this major AED (25). Recent data show that PHT-resistant rats from the kindling model of TLE have significantly higher expression of P-gp in capillary endothelial cells of the epileptic focus (the ipsilateral amygdala) than do PHT-responsive rats (26). In line with the multidrug-transporter hypothesis of epilepsy, overexpression of P-gp in BBB endothelial cells of PHT-resistant kindled rats is associated with loss of anticonvulsant efficacy of various AEDs that are substrates for P-gp (6). In PHT-resistant kindled rats, no increased P-gp expression was seen in brain regions adjacent to the focal tissue (26), potentially explaining that these rats lack the anticonvulsant effects, but not the adverse effects, of PHT (27). Overexpression of P-gp and MRPs in focal (i.e., epileptogenic) but not parafocal tissue also has been shown for patients with intractable TLE (24). The finding would explain why such patients exhibit the same central side effects of AEDs as do pharmacosensitive patients but lack the antiepileptic effect—that is, because uptake into epileptogenic brain tissue is reduced by overexpression of multidrug transporters.

In rats, pharmacologic inhibition of either P-gp or MRPs in the brain led to increased brain concentrations of various AEDs, suggesting that inhibition of multidrug transporters in the BBB could form a novel strategy for treatment of multidrug-resistant epilepsy (9,20). In a patient with intractable epilepsy in whom the P-gp inhibitor verapamil was added to the AED regimen, the addition greatly improved overall seizure control and subjective quality of life (28).

In animal models of TLE, subsequent to seizures, overexpression of P-gp occurs in a transient and regionally selective fashion in the brain, so that increased expression of this transporter is predominantly seen in regions, such as the hippocampus, thought to be involved in seizure initiation and propagation (6). Thus, the increased expression of P-gp and other multidrug transporters in such models appears to be a result of paroxysmal activity in specific brain regions. In addition to acquired (i.e., seizure-induced) overexpression of multidrug transporters, such as P-gp, overexpression may be intrinsic or constitutive, for example, as a result of polymorphisms in the *MDR1* (*ABCB1*) gene encoding P-gp (29). Thus, overexpression of ABC transporters could be involved in different patterns of multidrug resistance in epilepsy.

Unresolved Issues

Although the multidrug-transporter hypothesis of intractability is biologically reasonable and has attracted a great deal of interest, a number of open questions remain with regard to this hypothesis. First, not all AEDs are substrates for multidrug transporters, such as P-gp, so that the multidrug-transporter hypothesis does not explain pharmacoresistance to AEDs in general (6,9). Second, the molecular mechanisms underlying the overexpression of multidrug transporters in epileptogenic brain tissue are not sufficiently understood. As mentioned, experimental and clinical evidence suggests that increased expression of multidrug transporters, such as P-gp, may be either constitutive or acquired, for instance, as a result of frequent seizures. Such seizure-induced, regionally restricted overexpression of multidrug transporters may be a second-line defense mechanism of the BBB because of transient BBB opening during seizures and chronic dysregulation of BBB function, such as indicated by endothelial cell alterations, abnormal tight junctions, and thickening of the basal membrane in human epileptic tissue (6). Third, still limited proof exists that multidrug transporters are functionally important in human drug-resistant epilepsy (24). For direct proof of principle, it should be demonstrated that drug resistance could be reversed by adjunctive treatment with a P-gp and/or MRP inhibitor; to date, only anecdotal data are available in this respect (28). In principal, pharmacologic inhibition of P-gp or MRPs could form a novel clinical strategy to prevent and overcome drug resistance in patients with altered expression of multidrug transporters, but this theory requires validation.

Drug-target Hypothesis

Background Information

Another, more recent hypothesis to explain AED resistance in epilepsy is the drug-target hypothesis, which assumes that intrinsic or acquired loss of brain-target sensitivity is critically involved in resistance to AEDs. Again, this hypothesis is not restricted to epilepsy; rather, alterations in drug targets are assumed to be involved in pharmacoresistance to other diseases, such as cancer (30). With respect to epilepsy, the target hypothesis is principally based on studies with carbamazepine (CBZ) on voltage-gated sodium channels in hippocampal neurons. The primary mechanism of this major AED is well established and thought to be related to its action on voltage-gated Na^+ channels that are integral to the generation of seizure discharges (31).

Clinical and Experimental Data Supporting the Drug-target Hypothesis

Vreugdenhil and colleagues first reported that the modulation of sodium current inactivation by CBZ in hippocampal CA1 neurons from patients with TLE and mesial temporal lobe sclerosis was only half of that measured in neocortical neurons from the same patients and in CA1 neurons from patients without mesial temporal lobe sclerosis (32). More recently, these data have been substantiated and extended by Remy et al. (33). This study showed that the use-dependent block of

voltage-dependent Na^+ channels of dentate granule cells by CBZ is completely lost in patients with CBZ-resistant TLE in comparison to patients clinically responsive to this AED (33). In addition to the loss of use-dependent inhibition of Na^+ channels by CBZ, the fast recovery from inactivation of the fast Na^+ current was CBZ insensitive in pharmacoresistant patients, whereas recovery was markedly slowed in cells from CBZ-responsive patients (33). Based on these data, the authors suggested that a loss of Na^+ channel drug sensitivity might explain the development of drug-resistant epilepsy.

A loss of drug-target sensitivity also was found in rat models of TLE. In the kindling model of TLE, Na^+ channels of CA1 neurons isolated from the kindled hippocampus were only half as sensitive to the slowing of inactivation by CBZ compared with control rats (34). Consistent with data from neurons of patients with intractable TLE, Remy et al. (33) showed that use-dependent block of Na^+ channels of dentate granule cells by CBZ is absent in the pilocarpine rat model of TLE. Remy and colleagues (35) also demonstrated that the effect of PHT on the fast recovery from inactivation in hippocampal granule neurons was significantly reduced in the pilocarpine model, though not as pronounced as observed with CBZ. However, in contrast to CBZ and PHT, lamotrigine (LTG) slowed the time course of recovery from fast inactivation both in epileptic and control rats without significant intergroup difference (35). Valproate (VPA) did not appear to alter the fast recovery from inactivation of Na^+ channels in either experimental group (35). In contrast to these findings from dentate granule cells, slowing of fast recovery from inactivation of Na^+ channels by VPA has been described for CA1 neurons from both patients and rats (32,34). In these studies, this effect of VPA was not different between patients with or without mesial temporal lobe sclerosis or between kindled rats and controls.

To evaluate which molecular and functional changes in voltage-dependent Na^+ channels may underlie the lost or reduced pharmacosensitivity of these channels to CBZ and PHT in the pilocarpine model of TLE, Ellerkman et al. (36) studied the expression of Na^+ channel subunits. Both the ß1 and ß2 subunits were downregulated, indicating that Na^+ channel subunit composition changes may explain the altered pharmacosensitivity of Na^+ channels.

Unresolved Issues

Similar to the multidrug-transporter hypothesis, a number of open questions remain in regard to the drug-target hypothesis. First, it is not known whether the loss of Na^+ channel sensitivity to CBZ in hippocampal neurons of patients with refractory epilepsy extends to other AEDs. As indicated by the data of Vreugdenhil and colleagues, such a target alteration does at least not affect the action of VPA (32). Furthermore, as shown by the data from the rat model of TLE, although modulatory effects of CBZ and PHT on voltage-dependent Na^+ channels were lost or partially lost, LTG was efficacious in retarding recovery from inactivation of Na^+ channels in this model (35), although all three AEDs are thought to act by the same mechanism(s) (31). These observations from the pilocarpine model are not consistent with the clinical situation, because many patients who are resistant to CBZ or PHT are also resistant to LTG (3).

Second, whereas the studies on sodium channels of neurons from patients with epilepsy were performed in individuals with proven AED resistance, the rat experiments were performed in animals that were not preselected with respect to their response to AEDs. Both the kindling and pilocarpine models of TLE are known to respond to treatment with CBZ or PHT, so that rats from these models are not drug resistant per se (37,38). However, as shown previously (27,39), rats from both the kindling and pilocarpine models of TLE exhibit marked interindividual differences in AED responsiveness, so that it is possible to select AED responders and nonresponders from these models. For proof of principle of the target hypothesis, it would therefore be important to compare the pharmacosensitivity of Na^+ channels of responders and nonresponders selected from TLE models. Such a comparison has recently been published for the rat-kindling model (40). Responders and nonresponders were selected by repeated testing with PHT in vivo, followed by evaluation of the effects of PHT in vitro on Na^+ and Ca^{2+} channels of hippocampal CA1 neurons (40). PHT resistance was not associated with altered tonic block of Na^+ channels by PHT, but recovery from Na^+ channel inactivation and use-dependent blocking effects were not studied.

As a proof-of-principle for the target hypothesis, it will be important to demonstrate that AED-resistant subgroups of epileptic rats differ from AED-responsive subgroups in their AED-target sensitivity. Such a proof-of-principle is difficult to obtain in humans, because, in contrast to patients with intractable epilepsy, patients responding to AEDs usually do not undergo surgical treatment for their epilepsy. If the target hypothesis can be substantiated further, development of new AEDs that act specifically on these altered targets would be a novel and interesting strategy for treatment of intractable epilepsy. In this respect, it also is important to consider that, apart from voltage-dependent Na^+ channels, other drug targets may be altered in intractable epilepsy. One target of interest in this respect is $GABA_A$ receptors, which are involved in the antiepileptic effect of several major AEDs (31) and exhibit striking alterations in the epileptic brain (41–43).

Conclusions

Intrinsic or acquired resistance to AEDs is certainly a multifactorial phenomenon, and it would be naive to expect that

two hypotheses are sufficient to provide a complete explanation for intractability. Any neurobiologic theory of drug resistance in epilepsy must explain why, in medically refractory patients, AEDs cannot control the seizures, whereas other patients, with seemingly identical types of seizures or epilepsy, achieve control of seizures with the same AEDS. Both genetic factors and subclinical differences in epilepsy-related brain alterations may be involved. As in oncology, study of the basis of drug resistance in epilepsy may allow prediction of poor response to AED treatment and should offer new rational treatment approaches, for instance, by designing AEDs that are not targets for brain-expressed resistance mechanisms. It is likely that enhanced understanding of the mechanisms underlying multidrug resistance in epilepsy also will have an impact for the improved treatment of other brain diseases associated with interindividual differences in drug response, such as treatment-resistant depression, schizophrenia, brain tumors, and brain HIV (9).

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