Chapter 4
Molecular Mechanisms of Pharmacoresistant Epilepsy

Alberto Lazarowski and Liliana Czornyj

Abstract Epilepsy is a common neurological disorder and despite significant advances in therapy over recent decades, about 30–40 % of epileptic patients will remain refractory to pharmacological therapies despite optimized drug treatment. Taking a carefully reviewed definition of "drug-resistance" into account, two main concepts were proposed to explain the development of pharmacoresistance in epilepsy. The "target" hypothesis indicates that changes in the properties of the drug targets themselves may result in reduced sensitivity to antiepileptic drugs (AEDs). This hypothesis is supported by several pharmacodynamic modifications leading to loss of drugs' effects in refractory epilepsy. However, it cannot explain the refractoriness observed after polytherapeutic trials using several recommended AEDs at appropriate doses. Consequently, a mechanism of multidrug resistance (MDR) as previously described in cancer could also explain—at least in part—the reason for this particular phenotype. The so-called "transporters" hypothesis suggests that functional over-expression of multidrug transporters in brain could reduce AEDs access to the central nervous system. Both mechanisms could be active simultaneously in refractory epilepsy and possibly also, not represent the only mechanisms involved.

Keywords Refractory epilepsy • Target hypotheses • Pharmacodynamic • Antiepileptic drugs • Multidrug resistance • P-glycoprotein • ABC-transporters • Pharmacokinetics • Depolarized membrane

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4.1 Introduction

Epilepsy is one of the most common neurological problems and close to 3 % of individuals within the general population will have epilepsy during their lives. Both primary and secondary mechanisms are involved in the development of epileptic syndromes falling into two broad categories: generalized epilepsy (seizures begins simultaneously in both cerebral hemispheres) and partial epilepsy, characterized by localization-related seizures, originated in one or more foci, although they can spread to involve the entire brain (Benbadis 2001).

Despite considerable advances in pharmacotherapy, about 30 % of patients with epilepsy are refractory to pharmacotherapy (Temkin 2001). Seizures are not controlled in these patients in spite of several antiepileptic drugs (AEDs), even at maximum tolerated doses. This multidrug resistance phenotype (Fig. 4.1) may be present in the early stage of the disease (Elger 2003). Why does a subgroup of patients repeatedly fail to obtain seizure control with one AED after another? (Kwan and Brodie 2000). One explanation is that patients with epilepsy do not receive the correct treatment (Sisodiya 2005). Clinically, refractory epilepsy (RE) should be defined as the failure to achieve seizure freedom after a 9- or 18-month period of continued appropriate AEDs therapy in adults and children, respectively (Berg et al. 2001).

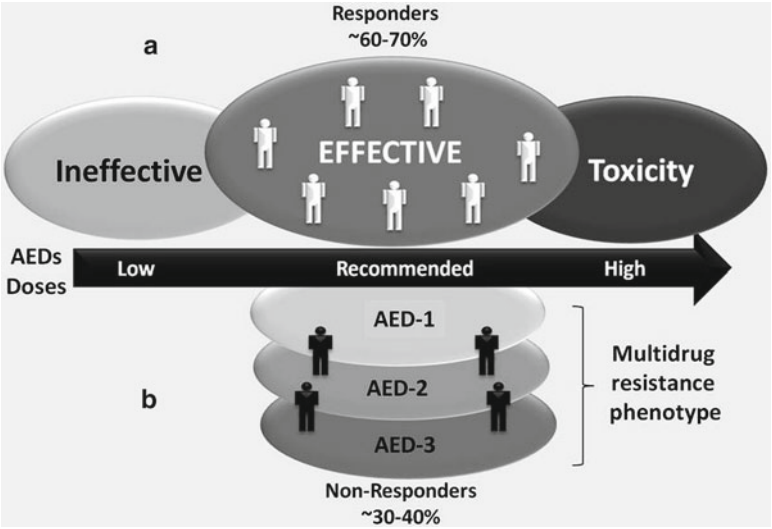

Fig. 4.1 Distribution of responder vs. nonresponder patients with multidrug resistance phenotypes. The *arrow* marks the administered escalating doses of AEDs. The *silhouettes* represent percentage of cases with each phenotype. (**a**) The typical distribution of the therapeutic response after the administration of appropriate AED (monotherapy): *Left*: insufficient dose (ineffective), *Center*: recommended dose (effective), and *Right*: high dose (toxicity). (**b**) The *lower part* represents the typical phenotype of patients refractory to treatment with three different AEDs, which all together are ineffective, even at doses inducing toxic effects

The following risk factors are considered important for the development of the RE phenotype.

- Age of the patient at the time of epilepsy onset
- Type and etiology of seizures
- Number and severity of seizures before the start of the treatment

In the presence of adequate doses and carefully monitored serum AEDs levels, drugs have to traverse the blood–brain barrier (BBB), achieve a sufficient minimum therapeutic concentration in the brain and activate specific target sites. According to this situation, two nonexclusive hypotheses have been postulated to explain refractoriness in epilepsy: the functional/structural modification of targets and/or the over-expression of drug-transporters in the brain (Remy and Beck 2006).

4.2 The Target Hypothesis or Pharmacodynamic Changes in Pharmacoresistance

After AEDs permeation into the central nervous system (CNS) parenchyma, drugs have to bind to one or more targets to exert their desired effects. Most AEDs predominantly target voltage-gated cathion channels (α-subunits of voltage-gated Na^+ channels and T-type voltage-gated Ca^{2+} channels) or influence gamma-aminobutyric acid (GABA)-mediated inhibition. Concerning this issue, genetic epileptic syndromes are secondary to mutations produced predominantly on ion channels, which are, in many cases, the same ion channels targeted by most AEDs (Kwan et al. 2001; Meldrum and Rogawski 2007) (Table 4.1).

Some AEDs potently inhibit low-threshold T-type Ca^{2+} channels, which are not expressed presynaptically, but are critically important in controlling excitability of the postsynaptic neuron compartments, both in normal and epileptic conditions. One such interesting pharmacodynamic change is observed as aberrant bursting in CA1 hippocampal neurons in epileptic animals mediated by an increased expression of T-type Ca^{2+} channels (Su et al. 2002) or in thalamic neurons implicated in the generation of spike-wave discharges in absence epilepsy (Huguenard 2002). This type of mechanism could also be applied to other voltage-gated ion channels such as K^+ channels (Remy and Beck 2006).

In humans, these types of modifications that reduce efficacy of a given AED at the "target" level were described in voltage-gated Na^+ channels by downregulation of their accessory β-subunits, altered α-subunit expression, or induction of neonatal Na^+ channel II and III α-isoform mRNAs (Aronica et al. 2001). Similar changes were observed in GABA-A receptors, by decrease of α_1-subunits and increase of α_4-subunits, reducing GABA and benzodiazepines (BZD) affinity for their receptor (Fig. 4.2). These mechanisms resulting in modifications of specific "targets" are associated with seizure activity, producing changes at the transcription level or alternative ion channel subunit mRNA splicing, as well as altered posttranslational

Table 4.1 Antiepileptic drug targets and their features as ABC-transporters (ABC-t) substrates

Antiepileptic drug	Voltage-gated Na^+ channels	HVA Ca^{2+} channels	LVA Ca^{2+} channels	GABA-A receptor	ABC-t substrate
Phenobarbital	–	Yes	–	–	P-gp
Phenytoin	Yes	–	–	–	P-gp/MRP
Carbamazepine	Yes	–	–	–	P-gp/MRP
Valproate	Possible	Possible	Possible	–	P-gp/MRP
Benzodiazepines	Yes	–	–	–	P-gp
Ethosuximide	Yes	–	–	–	–
Vigabatrin	Yes	–	–	–	P-gp
Lamotrigine	Yes	Possible	–	–	P-gp
Gabapentin	–	Possible	–	–	P-gp
Felbamate	Possible	Possible	Possible	Possible	P-gp
Topiramate	Possible	Possible	Possible	Possible	P-gp
Tiagabine	Yes	–	–	–	–
Oxcarbazepine	Yes	–	–	–	–
Levetiracetam	–	–	Possible	–	MRP
Pregabalin	Possible	–	–	–	–

P-gp P-glycoprotein, *MRP* multidrug resistant-associated proteins

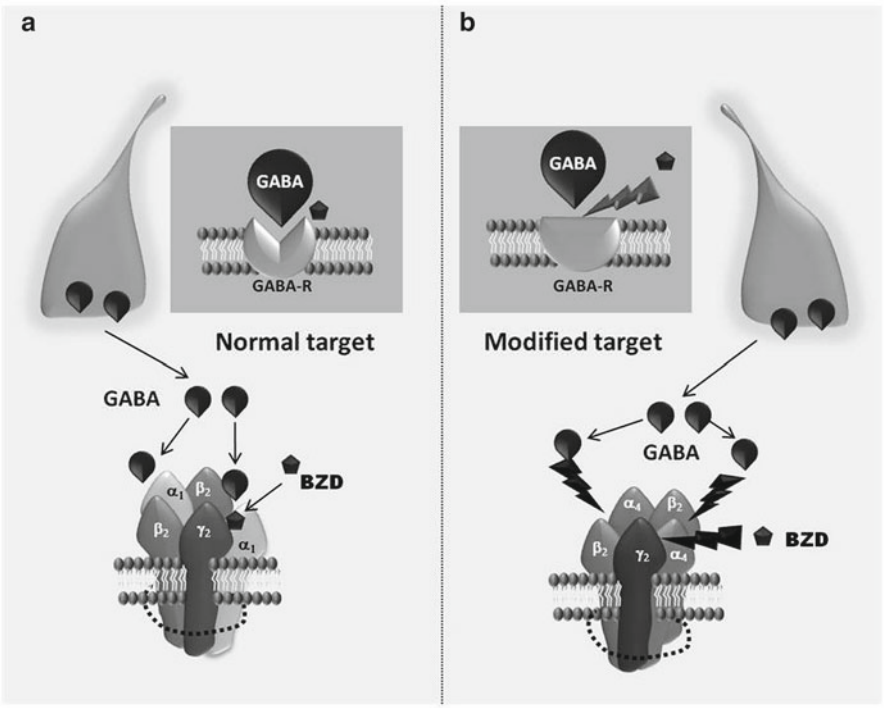

Fig. 4.2 Pharmacodynamic changes in the expression of GABA-R subunits during chronic epilepsies. The normal structure of the GABA-R expressing two α_1-subunits (**a**) can be modified by the expression of two α_4-subunits (**b**), producing a loss of sensibility to GABA and BZD

modification of the protein and/or phosphorylation by protein kinases. One intriguing question is that while carbamazepine, phenytoin (PHT), valproate, and lamotrigine bind to the same target (Na^+ channels) (Kuo 1998), reduced pharmacosensitivity to these drugs following pilocarpine-induced status epilepticus depends on the individual AED (Remy et al. 2003b). An explanation for this dissimilar altered sensitivity in epileptic tissue could be secondary to alterations of subunit composition of Na^+ channels. Indeed, AED-insensitive subunits or subunit combinations are promoted as has been observed in both human and experimental epilepsy (Remy and Beck 2006). Furthermore, downregulation of β1 and β2 accessory subunits of Na^+ channels, or changes secondary to alternative mRNA splicing of pore-forming subunits, have also been observed following induced status epilepticus in experimental models (Nicolas and Cau 1997; Aronica et al. 2001; Ellerkmann et al. 2003). Mutations of the β_1 subunit of Na^+ channels are the cause of generalized epilepsy with febrile seizures plus, an autosomal dominant epilepsy syndrome (Lucas et al. 2005). Interestingly, mutant β_1 subunits of this channel are associated with a dramatic and selective loss of use-dependent blocking effects by PHT (Lucas et al. 2005) and carbamazepine (Remy et al. 2003a, b). Collectively, these pharmacodynamic modifications resulting in loss of sensitivity (or increased refractoriness) have been termed "the target hypothesis of pharmacoresistance" (Remy and Beck 2006). However the "target hypothesis" cannot completely explain refractoriness to polytherapy.

4.3 The Transporters Hypothesis

The *transporters hypothesis* is an emerging concept of pharmacoresistance that is explained by an increased functional expression of multidrug transporter proteins, able to prevent access of AEDs to the brain and decrease concentration at their sites of action (Remy and Beck 2006; Lazarowski et al. 2007b; Löscher 2007; Potschka 2010). Multiple drug resistance (MDR) is a clinical phenotype characterized by insensitivity to a broad spectrum of drugs that presumably act on different mechanisms. Because most AEDs are administered orally, variations in genes related to drug absorption, transport and metabolism might modify the drug's plasmatic levels, body distribution, and access to the CNS. Enterocytes and hepatocytes express the major AEDs-metabolizing enzymes (CYP family), and multidrug transporters such as P-glycoprotein (P-gp), multidrug resistant-associated proteins (MRPs), and breast cancer resistant protein (BCRP). Their over-expression in these and other peripheral organs may play a crucial role by limiting drug absorption as well as regulating metabolism and excretion ratios, resulting in persistently low-AED plasmatic levels (Lazarowski et al. 2004a; Lazarowski and Czornyj 2011).

4.3.1 ABC-Transporters: Functions and Properties

Genes encoding transmembrane proteins that function as drug efflux pumps and belong to the ATP-binding cassette (ABC) transporter superfamily are classified into seven ABC[A-G] subfamilies (Dean et al. 2001). They export not only the drugs but also their metabolites, as well as xenobiotics and endogenous compounds of catabolism. Many transporters that were first characterized in excretory peripheral tissues have also been detected in the brain and are involved in the efflux of a variety of endogenous or exogenous substances (Lee et al. 2001).

Particularly P-gp (the product of MDR-1 gene), MRPs and BCRP, have been associated to the multidrug-resistant phenotype. Most ABC-transporters have two transmembrane domains (TM) and two cytosolic ATP-binding domains. BCRP has only one TM and one ATP-binding domain and is assumed to function as a dimmer (Fig. 4.3) (Dean et al. 2001).

Different agents, hormones, oncogenes, and transcription factors known to be involved in apoptosis, stress, inflammation, and hypoxia (COX-2, p53, NF-IL6, NFkB, AP-1, HIF-1α) (Bauer et al. 2008; Goldsmith et al. 1995; Cornwell and Smith 1993; Combates et al. 1994; Comerford et al. 2002) can upregulate the expression of these transporters in normally non-expressing cells such as neurons (Ramos et al. 2004; Lazarowski et al. 2007a) or cardiomyocytes (Laguens et al. 2007). This group of evidence suggests that P-gp and other MDR-like proteins may also be involved in biological processes related to survival-death mechanisms.

4.3.2 ABC-Transporters in Clinical Refractory Epilepsy

In normal brain, P-gp, MRPs, and BCRP are expressed in the BBB or the blood-cerebrospinal fluid (CSF) barrier (Girardin 2006) playing all together a combined role to reduce brain penetration of many dangerous compounds and drugs. P-gp is expressed on the apical side of the choroids' plexus epithelia, at the luminal membrane of vascular endothelial cells and at the astrocyte-foot-ending-processes of the BBB (Aronica et al. 2012). MRPs and BCRP are expressed in the microvessel endothelial cells of the BBB.

After the first description of P-gp over-expression in the brain of patients with RE (Tishler et al. 1995), several reports have shown high levels of P-gp and MRPs expression in epileptogenic brain areas obtained from patients with different RE syndromes. These studies indicate that P-gp is highly expressed not only in vascular endothelial cells but also in brain parenchymal cells (Lazarowski et al. 1999; Sisodiya et al. 1999; Dombrowski et al. 2001), in which they are not expressed under normal conditions (Lazarowski et al. 2004b).

Several authors have described the role of ABC-transporters in the development of pharmacoresistace in epilepsy (Sisodiya 2007; Lazarowski et al. 2007b; Löscher 2007). A recent review describes cerebral expression patterns of several classes of

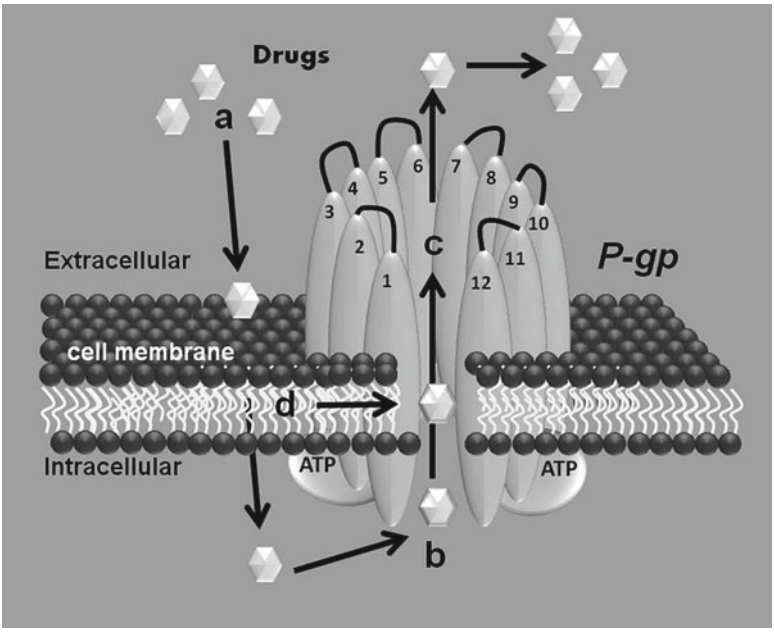

Fig. 4.3 Schematic representation of a typical structure of P-gp and sequential drug movement trough the cell membrane. P-gp is proposed to consist of two equivalent halves, each with six transmembrane segments and a nucleotide binding domain at the cytosolic side on each one. The 12 transmembrane helices together form a central cavity in the lipid bilayer. In the *left* side, it is shown how the extracellular drugs with high liposolubility access the cells (**a**). In the cytosol, drugs bind to the protein (P-gp) at an inward facing high-affinity site (**b**). This binding and hydrolysis of ATP initiate drug extrusion from the intracellular pool that will be expelled via a conformational change that transforms it to a low-affinity outward (extracellular) facing site, producing an active drug efflux (**c**). Alternatively, drugs can also be intercepted and extruded directly from the lipid bilayer (**d**)

ABC-transporters in the epileptogenic brain (Aronica et al. 2012). Over-expression of efflux transporter could be constitutive and exist before the onset of epilepsy, as suggested by the finding of upregulation of drug transporters in abnormal parenchymal cells in epileptogenic tissues from different RE syndromes, such as dysembryoplastic neuro-epithelial tumors, focal cortical dysplasias, hippocampal sclerosis, and cortical tubers (Sisodiya et al. 1999; Lazarowski et al. 2004c). However, they could also be over-expressed as a consequence of epileptic seizures (Seegers et al. 2002; Rizzi et al. 2002; Lazarowski et al. 2004b).

The inducible nature of ABC-transporter genes suggests that over-expression of these proteins can be observed in all excretory organs including BBB, playing a critical role in the modification of both systemic and local pharmacokinetics of AEDs. However, their induced expression in previously non-expressive cells as observed in brain parenchymal cells, particularly in neurons from epileptogenic areas (Aronica et al. 2003; Lazarowski et al. 1999, 2004a) suggests a differential

role related to the intrinsic convulsive mechanism, as previously proposed (Lazarowski et al. 2007b).

4.3.3 Experimental Evidences

Several epileptic (or convulsive) experimental models seem to firmly establish that some ABC-transporters, particularly P-gp, are over-expressed secondary to seizure activity. P-gp over-expression that depends on the frequency and intensity of seizures is related to a progressive increase of the pharmacoresistant phenotype [for review see Aronica et al. (2012)]. Furthermore, administration of a P-gp inhibitor such as tariquidar has been shown to revert drug resistance in animal models (van Vliet et al. 2006). Similarly, adjuvant treatment with nimodipine, a calcium channel blocker that also inhibits P-gp activity, is able to restore the normal hippocampal pharmacokinetics of PHT, an effect associated with seizure control (Höcht et al. 2007) avoiding death following repetitive convulsions in PHT-RE models (Lazarowski et al. 2007b). Complex mechanisms associated with excitotoxicity mediated by glutamic acid, including COX2-dependent inflammatory pathways (Bauer et al. 2008) or hypoxia-dependent HIF-1α activation are involved in the induction of P-gp brain over-expression (Ramos et al. 2004; Lazarowski et al. 2007a) and suggest that, even in the absence of seizures, the refractory phenotype could be induced in some epileptic syndromes. In this regard, a group of evidence indicates that P-gp can also decrease the plasma membrane potential of several cell types (Wadkins and Roepe 1997; Roepe 2000) and modify swelling-activated Cl^- currents (Vanoye et al. 1999), situations resulting from brain hypoxia and convulsive stress that may facilitate neuronal excitability.

All these evidences support the notion that induction of neuronal P-gp expression could correlate with a progressive acquisition of refractoriness associated with worsening of clinical features (Lazarowski et al. 2007b). This situation may support a third theory to explain pharmacoresistant epilepsy based on inherent phenotypic severity (Rogawski and Johnson 2008). In a previous study, we found that increased P-gp over-expression in brain of rats submitted to repetitive seizures was associated with membrane depolarization in fresh slices of hippocampus and neocortex, a situation reverted when nimodipine plus PHT were applied (Auzmendi et al. 2008). These results represent unique evidence supporting the notion that progressive P-gp over-expression contributes to membrane depolarization in hippocampus and neocortex, which may play a role in epileptogenesis and refractoriness.

The mechanisms underlying this silent process associated to a progressive functional over-expression of P-gp, particularly in neurons, could represent new therapeutic targets to control pharmacoresistant epilepsy (Hughes 2008; Robey et al. 2008; Potschka 2010).

4.4 Conclusions

Once each of the mechanisms leading to AED resistance are elucidated (target modifications and transporters over-expression), their knowledge may become increasingly important in new drug development and clinical applications. Novel effective treatment strategies to overcome pharmacoresistance would include not only new compounds for new cellular targets but also the development of novel AEDs that would not be substrates for efflux transporters. Regarding the properties of P-gp on membrane potential depolarization, the coadministration of drugs designed to avoid transporter over-expression or specific inhibitors of transporters function could prevent refractoriness and/or epileptogenesis, as suggested above.

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