

Chapter 2

Genes Involved in Pharmacoresistant Epilepsy

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Abstract This chapter is devoted to resistance to antiepileptic drugs (AEDs) and its genetic mechanisms. There are three general hypothesis proposed for pharmacoresistant epilepsy: (1) Target hypothesis, (2) Drug transporter hypothesis, and the (3) Intrinsic Severity Hypothesis (Gorter and Potschka, Jasper's basic mechanisms of the epilepsies, 4th ed. National Center for Biotechnology Information (USA), Bethesda, MD, 2012).

In diagnosing poor response to treatment, it is also important to separate drug resistance from incorrect diagnosis of epilepsy syndrome for example: (a) Epilepsy caused by mutations in Glucose transporter gene 1 (GLUT1) being treated with valproate (VPA) worsens the seizures in this disease whereas replacement of glucose with ketogenic diet alleviates seizures and the glucose deficit in the central

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nervous system. (Klepper, *Epilepsia* 49(Suppl 8):46–49, 2008; Klepper et al., *Neuropediatrics* 40(5):207–210, 2009) (b) Genetic or idiopathic epilepsies such as Childhood Absence Epilepsy (CAE), Juvenile Myoclonic Epilepsy (JME) and Dravet's Syndrome can be aggravated when treated with Na⁺ channel blockers (Genton, *Brain Dev* 22(2):75–80, 2000; Guerrini et al., *Epilepsia* 39(5):508–512, 1998; Thomas et al., *Brain* 129(Pt 5):1281–1292, 2006; Martínez-Juárez et al., *Brain* 129(Pt 5):1269–1280, 2006) and (c) Mitochondrial disorders can also be aggravated by VPA (Finsterer and Zarrouk Mahjoub, *Expert Opin Drug Metab Toxicol* 8(1):71–79, 2012).

Herein, we describe the three general hypothesis; we also summarize the “difficult to treat” genetic epilepsies.

Keywords Genes • Drug resistant • Epilepsy • Pharmacoresistant • Target hypothesis • Drug transporter

2.1 Target Hypothesis

A drug must have one or more actions on target sites of the brain to exert its therapeutic action. The resistance to drugs is caused by a structural or functional change at the site of action of drugs causing change in the pharmacodynamics of the drug (Sanchez-Alvarez et al. 2007).

The molecular targets refer to the sites that act as ligands of AEDs by which they exert their mechanism of action. These groups of molecules can be divided into two: voltage-gated channels and neurotransmitter receptors associated with neuronal excitation. These alterations at the site of action may be genetically determined or developed as a result of epigenetic and exogenous environmental factors.

2.1.1 Alterations of Sodium (Na⁺) Channels

Sodium channels are the main target of most AEDs, which act by blocking their resting phase (tonic block), preventing channel opening and Na⁺ conductance selectively. It has been suggested that mutations in Na⁺ channels may affect the clinical response to AEDs (Ragsdale and Avoli 1998).

The Na⁺ channels are formed by a pore-forming α subunit and two auxiliary associated subunits β . The modification of any of its subunits may play an important role in drug resistance (Sanchez-Alvarez et al. 2007).

The target theory was based on studies in voltage-regulated Na⁺ channel in hippocampal neurons with the use of carbamazepine (CBZ). Most antiepileptic drugs act blocking Na⁺ channels in their resting phase (tonic block), which prevents channel opening and ion conductance. It is considered that this alteration may be genetic

or acquired. An alteration in the Na⁺ channel can modify the sensitivity to one particular drug, but does not necessarily modify all responses to all drugs that share the same mechanism of action in the Na⁺ channel.

In genetic drug resistance, it is known that some mutations in genes encoding VGSC subunits may cause refractory or drug-resistant epilepsy (Claes et al. 2001). The *SCN1A* gene is located on chromosome 2q24.3; it has been linked to several diseases, including severe myoclonic epilepsy of infancy or Dravet Syndrome and Generalized Epilepsy with Febrile Seizure Plus (GEFS+). *SCN1A* gene encodes for the α subunit of the VGSC; however, an exact physiological basis of drug resistance related to structural alterations of the subunit of VGSC in Dravet Syndrome has not been demonstrated.

In the *SCN1A* gene, exon 5 encodes for one of the four voltage sensitive channel, the I-S4 domain. This has two versions, one neonatal (N) and another adult (A), which differ in three amino acids. Normally both exons are coexpressed in the adult brain. In studies by Tate et al. (Tate et al. 2005), a G to A polymorphism was identified in the *SCN1A* gene that affects the alternative splicing of exon 5. This polymorphism has been observed in the intron adjacent to exon 5. Apparently this region determines which sequence, either neonatal or adult, is incorporated into each channel. Ancestral allele G allows both exons to be expressed, whereas the mutant allele alters the expression of neonatal exon by interrupting the consensus sequence, reducing the expression of this exon relative to exon 5A. By studying the minimum dose required of two AEDs, namely, CBZ and phenytoin (PHT) prescribed in 706 patients, Tate et al. (2006) found that AA homozygotes had an average dose of CBZ and PHT higher than that of heterozygotes, and the latter also had higher dose than GG homozygotes. A second study by the same authors failed to report this association; therefore, more studies are needed to confirm this (Tate et al. 2006).

An association between polymorphisms of the *SCN2A* gene channel, which codes for the $\alpha 2$ subunit of neuronal Na⁺ channel, and resistance to drugs acting on Na⁺ channels has also been found (Kwan et al. 2008).

The β subunits function is to modulate the membrane expression of the Na⁺ channel. A mutation in the gene encoding for the $\beta 1$ subunit has been linked with GEFS+. In epilepsy animal models a decreased expression of $\beta 1$ and $\beta 2$ subunit has been found. However, this lack of effect of CBZ on Na⁺ channels in kindled rats is transient, and the inhibitory effect of CBZ on Na⁺ channels is recovered. This effect has not been described in vivo (Gastaldi et al. 1998; Ellerkmann et al. 2003).

In acquired drug resistance, exogenous factors such as the presence of repeated seizures can promote transcriptional or post-transcriptional changes capable of inducing structural changes in VGSC, changes that are enough to induce refractory or drug-resistant epilepsy (Beck 2007). Remy et al. (2003) observed in brain tissue, from patients undergoing surgery for temporal lobe epilepsy with hippocampal sclerosis, a tonic loss of VGSC blockade, in contrast to the CBZ sensitive patient tissue samples.

2.1.2 Alterations of Voltage-Dependent Calcium (Ca^+) Channels

The Ca^+ channels are voltage transmembrane ion channels with an excitatory function. There are at least six types of Ca^+ channels (T, L, N, P/Q, R) classified in two categories on the basis of the voltage necessary for activation: low threshold and high threshold. The T-type channel is the only low-threshold Ca^{2+} channel current described (Shin et al. 2008).

Each VGCC is formed by an $\alpha 1$ subunit which serves as main pore and sensor in potential change, which is encoded by ten distinct genes, and several accessory subunits identified as β , γ , and $\alpha 2\delta$ subunits. The VGCC has a highly functional heterogeneity as a result of its wide distribution.

The T-type calcium channels are involved in generating thalamocortical discharges, involved in the pathophysiology of absence seizures. The $\alpha 1\text{G}$ subunit of T-type calcium channels is related to the generation of spike and wave discharges, while the $\alpha 1$ subunit does not have this physiological property. Therefore, it is possible that an imbalance in the proportion of $\alpha 1$ and $\alpha 1\text{G}$ subunits in the T Ca^+ channel reduces the response to anti-absence AEDs such as ethosuximide (ESM), lamotrigine (LTG), VPA, and zonisamide (ZNS). However, there is not experimental evidence yet to confirm this hypothesis (Chioza et al. 2001).

2.1.3 Alterations of Gamma Aminobutyric Acid Channels

Gamma Aminobutyric Acid (GABA) is the major inhibitory neurotransmitter in the adult brain. There are two GABA receptors: GABA_A and GABA_B . The GABA_A receptor has specific binding sites for benzodiazepines and barbiturates. GABA_A channels mediate most inhibitory neurotransmission in the brain. Most GABA_A channels are assembled by seven different subfamilies, which are defined by similar sequences: α , β , γ , δ , π , θ , and ρ . Most of the GABA_A channels are formed by α , β and γ subunits. The 60 % of GABA_A subunits are assembled by $\alpha_1\beta_2\gamma_2$ subunits. The GABA_A receptor subtypes are distinguished by their affinity for GABA, channel kinetics and the rate of desensitization, distribution and pharmacology. Changes in the composition of the channel may have implications on its role and sensitivity to AEDs, especially of benzodiazepines (Schmidt and Löscher 2005).

In some animal models of chronic epilepsy there has been a progressive decrease in GABA receptor response to benzodiazepines. In these models hippocampal neuronal loss has been observed and has been associated with recurrent seizures with the subsequent development of acquired resistance, secondary to altered GABA_A receptor. Combined molecular and functional studies indicate that the transcriptional change occurs in the α subunit of the GABA_A receptor, consistent with a decrease in the α_1 subunit expression and an increase in the α_4 (Brooks-Kayal et al. 1998).

2.2 Multidrug Transporter Hypothesis (See Fig. 2.1)

The multidrug transporter hypothesis is based on the modification of the drug pharmacokinetics causing an inadequate concentration of antiepileptic drugs in brain tissue. This phenomenon occurs by an increase in cell membrane proteins which expel the endogenous toxins and xenobiotics, thus preventing penetration the blood–brain barrier and a decreased concentration of the medications at the epileptogenic focus or zones.

Drug resistance that occurs as a result of an increase in membrane proteins has become evident in several diseases such as cancer and epilepsy. Now it is considered a major cause of treatment failure. Resistance may be evident from the start of therapy or after an adequate initial response. There may even be cross-resistance to several drugs as a result of overexpression of membrane transport proteins. This phenomenon is called multidrug resistance (MDR).

These proteins are expressed at the luminal surface of cells that form the blood–brain barrier, glial and endothelial cells, and neurons, thus acting as a “second barrier”. This would explain why, despite the use of AEDs at maximum doses, these are not effective in patients with refractory or drug-resistant epilepsy (Dombrowski et al. 2001).

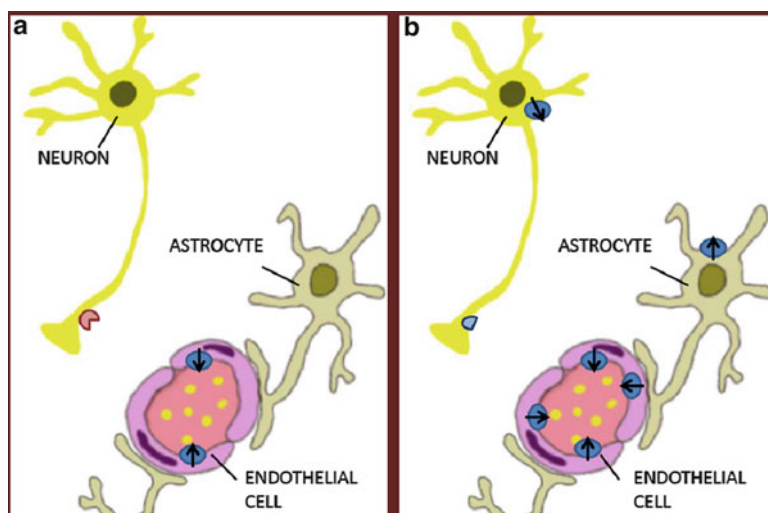


Fig. 2.1 (a) Schematic representation of blood brain barrier and normal expression of multidrug transporters. Expression of normal ion channel. (b) Epileptogenic-brain tissue with multidrug transporter overexpressed in capillary endothelial cells, astrocytes and neurons. Expression of mutated ion channel

2.2.1 ABC Superfamily (ATP-Binding Cassette Transporters)

The ABC proteins are associated with multiple drug resistance. These are members of an energy-dependent protein superfamily. Several members of the superfamily have been identified and classified into seven subfamilies (ABCA, ABCB, ABCC, ABCD, ABCE, ABCF, and ABCG). Among these, the subfamilies ABCB, ABCC, and ABCG are involved in MDR.

The ABCB1 (*MDR1*) and its protein, P-glycoprotein (P-gp) were the first ones to be described and are the most studied among those associated with resistance to multiple drugs. The *MDR1* gene is located on chromosome 7q21.1. The P-gp is a membrane protein with 1,280 amino acids and sized/weighing 170 kDa. It is found in different tissues with excretory or secretory function, such as liver, pancreas, kidney, intestine, and others. Substances that interact with P-gp are very diverse and have great ability to cross plasma barriers for their characteristics: high molecular weight, positive charge, and high lipophilicity (Kwan and Brodie 2005).

Tishler et al. (1995) suggested that the poor response to AED treatment in patients with refractory epilepsy was secondary to a reduction in the penetration of the drugs to the central nervous system. They observed an increased expression of *MDR1* mRNA in 11 of 19 brain tissue of patients undergoing surgery with an increase in P-gp immunostaining. The concentration of PHT in cells was reduced to ¼ in patients expressing *MDR1* in contrast to those that did not express it.

The variable expression of P-gp suggests a genetic influence, environmental factors or both. *MDR1* gene is highly polymorphic. More than 50 single nucleotide polymorphism (SNP) along with insertion/deletion polymorphisms have been reported in the *MDR1* (ABCB1) gene that encodes P-gp. Environmental factors could cause the expression of *MDR1* in tissues where it was not previously found; this could explain the fact that symptomatic epilepsies are more resistant to AEDs than idiopathic or genetic epilepsies (Kwan and Brodie 2000, 2005).

An increased expression of multidrug transporters has also been associated with constitutive, genetic or hereditary mechanism. Increased expression of *MDR1* was demonstrated in endothelial cells of the blood–brain barrier up to 130 % in patients with epilepsy, *MRP5* was increased up to 180 % and *MDR2* up to 225 % in comparison to patients without epilepsy (Dombrowski et al. 2001). Siddiqui et al. (2003) reported an association between drug resistance in epilepsy and a polymorphism in the ABCB1 gene. They reported that patients with the CC genotype expressed more P-gp, which was associated with increased drug resistance versus patients with the TT genotype. However, this association has been poorly reproduced and other studies have even documented an inverse association (Tan et al. 2004; Sills et al. 2005).

The association of drug-resistant or refractory epilepsy and some specific etiologies, including mesial temporal sclerosis, cortical dysplasias, and glial tumors has been known now for some time (Semah and Ryvlin 2005). Overexpression of multidrug resistance protein is regionally selective areas, affecting mainly epileptic brain areas. Overexpression of *MRP1* and *MDR1* was demonstrated in perivascular astrocytes of patients with temporal lobe epilepsy due to hippocampal sclerosis.

An aberrant expression in neurons and glial cells was observed as well in patients with dysembryoplastic neuroepithelial tumors and malformation of cortical development (Sisodiya et al. 2002; Sanchez-Alvarez et al. 2007).

It has been proposed that sustained augmentation of glutamate secondary to seizures is the mechanism of acquired increased P-gp expression in cells of the blood–brain barrier. Glutamate acts through NMDA-R, which produces the signal for arachidonic acid, which is then oxidized by the cyclooxygenase 2 (COX-2) producing prostanoids, including prostaglandin E2 (PGE2). PGE2 acts on the Prostaglandin E receptor 1 (EP1-R), which by means of a second messenger system increases transcription of P-gp (Potschka 2012).

Among the drugs transported by P-gp are CBZ, felbamate (FBM), gabapentin (GBP), LTG, phenobarbital (PB), PHT, and topiramate (TPM). Levetiracetam (LVT) and benzodiazepines are not substrates of P-gp in the blood–brain barrier. Kwan et al. (2010) reported a negative relationship between seizure control after epilepsy surgery and P-gp expression on the resected tissue of patients. Various antiepileptic drugs, their mechanisms of action and their corresponding transporters are shown on Table 2.1.

2.3 Intrinsic Severity Hypothesis

A prognostic factor associated with drug-resistant epilepsy is the frequency of seizures at the beginning of the disease, in some cases associated with the number of seizures before the start of treatment (Kwan and Brodie 2000). Even some cases of drug-resistant epilepsies had prolonged episodes of remission in its initial phases. The intrinsic severity hypothesis implies that the frequency of seizures is associated with refractoriness: if seizures are easy to trigger, then seizures will be more difficult to suppress, and the usual dose of the drug will not be enough. There is as yet no evidence that genetic factors directly contribute to the severity of epilepsy in idiopathic (genetic generalized epilepsies, Rogawski and Johnson 2008).

2.4 Genetic Epilepsies “Difficult to Treat”

Pathogenic alterations or mutation in genes and structural abnormalities in chromosomes (deletions, insertions) are responsible of a variety of epilepsies. In some, the possibility of drug-resistant epilepsy is high.

Several mechanisms may be interrelated between genetic disorders and the presence of epilepsy. It is important to distinguish between the susceptibility to generate epilepsy caused by a functional abnormality of a gene, and epilepsy that results from structural or functional abnormalities in a chromosome. Some genetic disorders relate more to certain types of epilepsy but overall any seizure type may be present.

Table 2.2 summarizes some genetic pharmacoresistant epilepsies.

Table 2.1 Antiepileptic drugs, their mechanisms of action and their corresponding transporters

Antiepileptic drug	Mechanism of action					Transporter					
	Blockade of Na ⁺ channel	Blockade of T-type Ca ⁺ channel	Blockade of other Ca ⁺ channels	Blockade of K ⁺ channel	GABA agonist	Glutamine antagonist	SV2A Action	P-glycoprotein	MRP	MDR	Target
Carbamazepine	+	-	+	-	+	+	-	+	+	+	+
Clobazam/Clonazepam	+	-	+	-	+	-	-	?	?	-	+
Ethosuximide	-	+	-	-	-	-	-	-	?	?	?
Felbatame	+	-	+	-	+	+	-	+	-	+	?
Gabapentin	+	-	+	+	+	+	-	+	?	+	?
Lamotrigine	+	-	+	+	-	+	-	+	-	+	-
Levetiracetam	-	-	+	+	+	-	+	-	-	-	?
Oxcarbazepine	+	-	+	+	-	+	-	+	?	?	?
Phenobarbital/Primidone	+	+	+	-	+	+	-	+	-	-	+
Phenytoin	+	-	+	-	+	-	-	+	+	+	+
Pregabalin	-	-	+	-	-	+	-	?	?	?	?
Topiramate	+	-	+	+	+	+	-	+	?	+	?
Valproate	+	+	+	-	+	+	-	?	+	+	-

+ = effect
- = no effect
? = unknown

Table 2.2 Genetic pharmacoresistant epilepsies

	Disease	Phenotype	Genotype	References
Genes involved in drug resistant epilepsy	Dravet syndrome	Normal development before onset Seizures initially induced by fever. Begin during first year of life Ataxia, mental decline EEG normal initially, generalized spike-wave activity	<i>SCN1A</i> , <i>SCN9A</i> , <i>GABRG2</i>	Dravet (1978), Ohmori, Ouchida, Ohtsuka, Oka and Shimizu (2002), Singh et al. (2001), and Harkin et al. (2007)
	Lafora disease	Insidious onset of progressive neurodegeneration, myoclonic jerks, generalized seizures, and often visual hallucination. Progressive cognitive decline resulting in dementia. Lafora bodies	<i>NHLRC1</i> , <i>EMP2A</i>	Chan et al. (2003) and Ganesh et al. (2002a, 2002b)
	Unverricht-Lundborg disease	Begin between 6 and 13 years of age. Stimulus sensitive myoclonic jerks, ataxia, incoordination, tremor, dysarthria. The disease stabilizes in early adulthood. No cognitive decline	<i>CSTB</i>	Shahwan et al. (2005)
	Pharmacoresistant MTLE with HS ^a	Febrile seizures, complex focal seizures. Epigastric aura, fear and orolimentary automatisms	<i>ABCB1</i>	Kubota et al. (2006)
Genetic alterations associated with drug resistant epilepsies	GLUT1 deficiency syndrome	Infantile-onset epileptic encephalopathy, microcephaly, incoordination and spasticity. Hypoglycorrhachia (<40 mg/dl) and low lactate	<i>SLC2A1</i>	Klepper and Voit (2002)
	Tuberous sclerosis	Hamartomas in multiple organ systems, epilepsy, autism, behavioral problems, angiomyolipomas, pulmonary lymphangioleiomyomatosis, melanotic macules, facial angiofibromas	<i>TSC1</i> , <i>TSC2</i>	Povey et al. (1994)

(continued)

Table 2.2 (continued)

Chromosomal alterations associated with drug resistant epilepsies	Disease	Phenotype	Genotype	References
	Ring chromosome 20 syndrome	Behavioral restlessness and aggression Mental retardation appearing after apparently normal development in a child without dysmorphic features Atypical absence status with diffuse 2–3 Hz slow waves and spikes of possible mesial frontal origin	Ring20	Canevini et al. (1998)
	Fragile X	Learning disorders, hyperactive, autistic child delayed speech, hypotonic, hyperelastic joints, macroorchidism, narrow, long face, large ears with small mandibles and focal epilepsy	Xq27.3	Fu et al. (1991)
	Miller Dieker	Lissencephaly microcephaly, facial dysmorphism, cardiac malformations, growth retardation, mental deficiency, hypotonia and intractable seizures. EEG: focal or multifocal spike-wave discharges, bisynchronous bursts of diffuse paroxysmal activity, and high-voltage diffuse rhythmic theta and beta activity	17p13.3, Deletion or mutation in <i>LIS 1 gene</i>	Miller (1963) and Dobyns et al. (1993)
	Angelman syndrome	Mental retardation, microcephaly, movement disorder, abnormal behaviors, and severe alterations in language. Myoclonic jerks, focal and generalised status epilepticus	Maternal deletion on 15q11–q13	Angelman (1965) and Minassian et al. (1998)
	Prader Willi syndrome	Hypotonia, obesity, mental retardation, short stature, hypogonadotropic hypogonadism, and seizures	Paternal deletion <i>SNRPN gen</i>	Cassidy et al. (1984)

^aMesial temporal lobe epilepsy with hippocampal sclerosis

2.5 Conclusions

2.5.1 *Limitations of the Three Hypothesis*

To prove a given drug resistance theory, it is important to show that the subgroup of patients with drug resistance has differences in their receptors in comparison to those of responders. However, this is difficult to achieve because patients who respond to drugs are not subjected to epilepsy surgery. Any proposed mechanism for drug resistance must meet the following requirements to be considered valid: be detectable in epileptic brain tissue, have a pathophysiological mechanism, demonstrable in human epilepsy and, when modified, must affect the phenomenon of drug resistance (Sisodiya 2003).

The fact that most patients are resistant to multiple treatments, including several AEDs with different mechanisms of action, suggests that other less specific or unknown mechanisms with some commonality about AED cellular or network actions contribute to drug resistance or that more than one mechanism may be involved (Löscher et al. 2006). Some changes were induced only transiently in animal models of epilepsy which do not necessarily explain chronic pharmacoresistance (Van Vliet et al. 2005; Löscher 2007).

According to Schmidt and Löscher, (2009) the intrinsic hypothesis lacks studies and “a subgroup of patients with a higher seizure frequency at the onset of treatment will become seizure-free but require higher serum concentrations of AEDs to do so than those with a lower seizure frequency”.

2.5.2 *How to Define Genetic Drug-Resistant Epilepsies?*

We have collected over a thousand patients with CAE, JME and CAE evolving to JME, Lafora disease, GEFS+, and Angelman Syndrome. These epilepsies respond variably to AED therapy, depending on their molecular lesion.

This chapter leads us to the question—what is the definition of genetic “drug-resistant” epilepsies. In the end we propose two assertions: (1) epilepsies are drug-resistant because the AED does not have an effect on the specific molecular lesion of the epilepsy syndrome. The epilepsy is supposedly “drug resistant” but seizures do not stop because “the key does not fit the lock in the door” and (2) when the AED has a proven effect on the molecular lesion but seizures persist in spite of AED treatment; this latter, we believe is true genetic pharmacoresistant epilepsy. Therefore, we favor the “intrinsic disease” mechanisms as an explanation for the resistance in genetic epilepsies (Fig. 2.2).

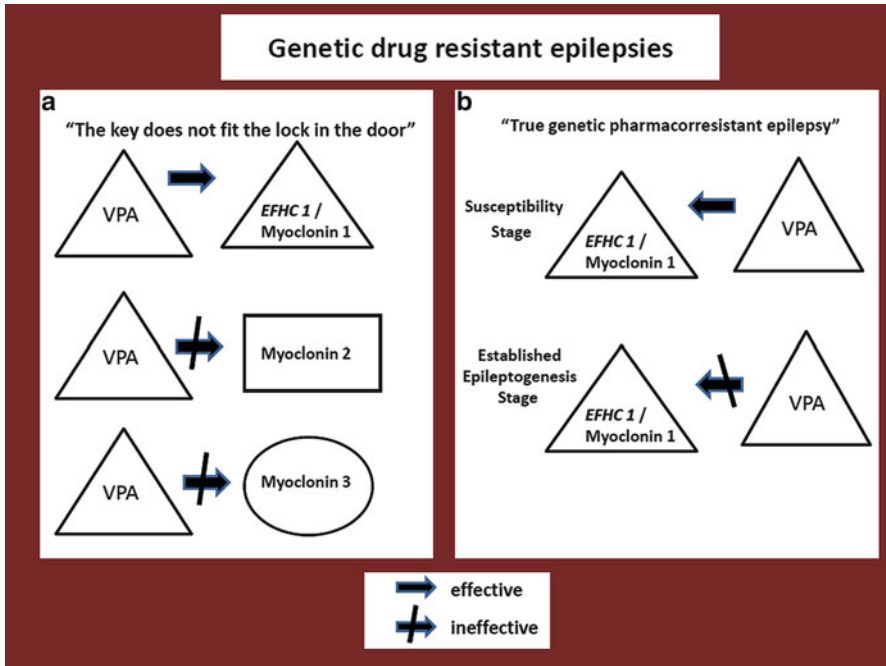


Fig. 2.2 (a) *EFHC1*/Myoclonin mutations in Juvenile Myoclonic Epilepsy (JME) frequently respond to treatment with valproate (VPA), however other JME mutations (illustrated as: Myoclonin 2 and Myoclonin 3) might not achieve seizure control due to a different molecular lesion unresponsive to VPA therapy. (b) *EFHC1*/Myoclonin mutations in a susceptibility or early stage respond adequately to VPA treatment whereas in established epileptogenesis drug resistance is seen even though the same molecular lesion is present; therefore a true genetic pharmacoresistance is encountered

2.5.3 Future Directions

The question is how to attack the problem in patients. A recommended step now, in assessing AED use, is to genotype epilepsies and use the genotype to guide AED use.

It would be ideal to perform a whole or large scale pharmacogenomic study of how AEDs effects are genetically determined in order to look for responders and non-responders and also for patients that will develop side effects from a specific AED. A large-scale pharmacogenomic studies could also be done in patients who were submitted to surgery for drug-resistant epilepsy. We could study the surgical specimens for their neuropathologic and biochemical abnormalities and correlate the findings with whole genome sequencing.

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