DRUG RESISTANT EPILEPSY

Review Submitted for Partial Fulfillment of
Master Degree in Neuropsychiatry

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2010
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INTRODUCTION

In many patients with epilepsy, seizures are well-controlled with currently available anti-epileptic drugs. However, seizures persist in a considerable proportion of these patients (Remy and Beck, 2006). It is estimated that 20-25% of the epileptic patients fail to achieve good control with the different anti-epileptic drug treatments, developing refractory epilepsy (Lazarowski et al., 2007).

It is not known why and how epilepsy becomes drug resistant in some patients while others with seemingly identical seizure types and epilepsy syndromes can achieve seizure control with medication (Schmidt and Loscher, 2005).

The causes of drug resistant epilepsy are numerous, many due to abnormalities in brain maturation, severe brain injuries with resultant irreversible changes to cerebral neuroglial organization and inhibitory neuron function, kindling phenomenon, seizure-induced disturbances of oxygen supply, as well as acquired (or hereditary) changes in transporter proteins of the blood-brain barrier which function in the efflux of anti-epileptic drugs from the brain (Awasthi et al, 2005).

Several hypotheses have been formulated to explain the pathogenesis of drug resistance in epilepsy:
1. The drug fails to reach the neuronal target (transporter hypothesis). This includes the cerebrovascular overexpression of multidrug transporter proteins.

2. The drug fails to act at the neuronal target (target hypothesis). (Marchi et al., 2010)

Regarding transporter hypothesis, analysis of multidrug transporter expression in human and experimental epilepsy has favored the concept that increased levels of these transporters are present in epileptic tissue, thus lowering intraparenchymal drug concentrations and rendering several anticonvulsant drugs less effective (Remy et al., 2003a).

The abnormal parenchyma cells present in the epileptogenic tissues from different refractory epilepsy syndromes, such as dysembryoplastic neuroepithelial tumors, focal cortical dysplasia and hippocampal sclerosis, could express multidrug transporters P-gp or MRP1 constitutively (Sisodiya et al., 2002).

According to the target hypothesis, pharmaco-resistance occurs when target sites are structurally and/or functionally modified in such a way that they become less sensitive to anti-epileptic drugs. A large number of targets for anti-epileptic drugs have been identified in the brain, many of which undergo molecular changes during chronic epilepsy. So far, a reduced sensitivity of drug targets to anti-epileptic drugs in chronic human and experimental epilepsy has been suggested for the voltage-gated Na+ channel and the GABA\textsubscript{A} receptor.
Cumulative evidence suggests that there is reduced pharmacosensitivity to Na+ channel-acting drugs in patients with intractable temporal lobe epilepsy (Remy et al., 2003a).
At the molecular level, altered drug targets may arise due to the transcriptional regulation of ion channel subunit genes. It has become clear over the recent years that seizures cause coordinated and cell-specific transcriptional changes that result in either an up- or down-regulation of families of ion channel mRNAs. This, in turn, causes alterations in the subunit composition or density of ion channels, resulting in altered intrinsic and synaptic neuronal properties (Beck, 2007).
AIM OF THE WORK

Our aim is to explore the pathological mechanisms underlying drug resistance in epilepsy and to search reviews trying to explain how and why drug resistance occurs in some patients with epilepsy to reach better management of these patients.
DEFINITION, INCIDENCE AND RISK FACTORS

Although many new antiepileptic drugs have been developed in the past decade, epilepsy remains resistant to drug therapy in about one-third of patients. Approximately 20% of patients with primary generalized epilepsy and up to 60% of patients who have focal epilepsy develop drug resistance during the course of their condition, which for many is lifelong (Siegel, 2004).

Considering that epilepsy is one of the most common chronic neurologic disorders, drug-resistant epilepsy is a major public health problem. The consequences of drug-resistant epilepsy can be quite severe, including mortality rates that are 4 to 7 times higher in people with drug-resistant seizures. It is not known why and how epilepsy becomes drug resistant in some patients while others with seemingly identical seizure types and epilepsy syndromes can achieve seizure control with medication (Schmidt and Loscher, 2005).

People with pharmaco-resistant epilepsy are about 2 to 10 times more likely to die compared with the general population. The risk is inversely linked to seizure control. “Sudden unexpected death in epilepsy” is the most frequent
type of death in patients with pharmaco-resistant epilepsy. This category excludes deaths from trauma or drowning. Case-control studies have shown that the risk of sudden unexpected death is closely and inversely associated with seizure control; the rate is significantly higher in patients who have a higher frequency of convulsive seizures. In addition, freedom from seizures, achieved after successful epilepsy surgery, reduces the risk of death from all causes (Pati and Alexopoulos, 2010).

Despite advances in anti-epileptic drug therapy and epilepsy surgery in recent years, intractable epilepsy remains a major clinical problem. An important characteristic of medically intractable (pharmaco-resistant) epilepsy is that most patients with refractory epilepsy are resistant to several, if not all anti-epileptic drugs, even though these drugs act by different mechanisms (Kwan and Brodie, 2000).

During treatment with a variety of different anti-epileptic drugs, as many as 20–40% of newly treated patients with epilepsy will not enter long-term remission for several years and despite medical management with modern Anti-epileptic drugs, a number of these patients continue to have drug-resistant epilepsy with frequent debilitating seizures (Schmidt and Loscher, 2005).
The exact fraction of epilepsy patients who are considered refractory varies in the literature, mostly because the criteria for classification as pharmaco-resistant have varied. A substantial proportion (about 30%) of epilepsy patients do not respond to any of two to three first line Anti-epileptic drugs, despite administration in an optimally monitored regimen (Remy and Beck, 2006).

Although no single accepted definition exists of drug resistant epilepsy, different definitions may be appropriate, depending on the type of seizure and epilepsy syndrome and the purpose for which the definition is used. Definitions usually include the number of anti-epileptic drug failures and the minimal remission or seizure frequency during a specified duration of therapy (Schmidt and Loscher, 2005).

The different definitions of refractoriness emerge depending on the context. All are based on the 3 main components of intractability: number of Anti-epileptic drugs previously taken, frequency of seizures and duration of non-controlled epilepsy (Beleza, 2009).

In investigational studies, criteria of refractoriness include: (1) absence of response to 2 Anti-epileptic drugs tolerated at reasonable doses; (2) minimum frequency of
seizures (e.g. 1 seizure per month) to be considered refractory or the duration of minimum remission (e.g. 6-12 months) to be qualified as nonrefractory, and (3) duration of 1 year to 1 decade of non-controlled epilepsy. Depending on the criteria applied, the frequency of refractory epilepsy varies from 10 to 37.5% (Kwan and Brodie, 2000).

A flexible scale of refractoriness has been developed for clinical use and classifies epilepsy as potential (no seizure freedom with Anti-epileptic drugs taken less than 1 year and predictive factors for refractoriness), probable (no seizure freedom more than 1 year with at least 2 Anti-epileptic drugs) or definitely refractory (catastrophic epilepsy or no freedom of seizure for more than 1 year after 5 years of treatment with at least 3 Anti-epileptic drugs) depending on the duration of epilepsy and medical treatment, seizure control and number of Anti-epileptic drugs used. A sub-classification of refractoriness as acceptable or unacceptable was also included, taking into account the patients' impression of the impact of epilepsy (seizures, co-morbidity and adverse effects of Anti-epileptic drugs) on their quality of life (e.g. a patient with acceptable refractory epilepsy presenting infrequent nocturnal seizures may become definitely refractory with the occurrence of diurnal generalized tonic-clonic seizures affecting employment, education and driving) (Starreveld and Guberman, 2006).
It is mandatory to exclude false refractoriness related to non-epileptic seizures, inadequate anti-epileptic drugs, noncompliance and seizure-precipitating factors. Video-EEG monitoring is an essential tool in this process, aiming to perform a differential diagnosis of paroxysmal events and a correct classification of seizures and epileptic syndromes. Non-epileptic events more frequently found include cardiovascular syncopes sleep diseases and psychogenic events (Beleza, 2009).

False pharmaco-resistance may not be easily recognizable, and this possibility needs to be investigated in any patient presenting with difficult-to-control seizures. Up to 30% of patients referred to clinics with a diagnosis of pharmaco-resistant epilepsy may have been misdiagnosed, and many can be helped by optimizing their treatment. Causes of false pharmaco-resistant epilepsy include misdiagnosis of epilepsy (i.e. patients with psychogenic non-epileptic seizures misdiagnosed and inappropriately treated with multiple antiepileptic drugs), misdiagnosis of epilepsy type leading to inappropriate drug selection (i.e. misdiagnosis of temporal lobe seizures for absence seizures, or vice versa), Inappropriate assessment of response or lack of response (i.e. drug interactions leading to increased side effects and decreased tolerability), Inappropriate dosage and inappropriate patient behavior (i.e. poor compliance) (Pati and Alexopoulos, 2010).
Based on partly prospective clinical observations in a series of patients with newly diagnosed epilepsy, those who did not achieve complete seizure control for 12 consecutive months with the first two or three Anti-epileptic drugs were given the predictive diagnosis of refractory or drug-resistant epilepsy (Kwan and Brodie, 2000).

In general, many experts would agree that whenever a patient does not become seizure free for 12 months during long-term treatment with several suitable Anti-epileptic drugs at maximal tolerated doses, the epilepsy can be broadly classified as drug-resistant, pharmaco-resistant, or medically refractory (Schmidt and Loscher, 2005).

Refractory epilepsy is established when there is inadequate seizure control despite using potentially effective Anti-epileptic drugs at tolerable levels for 1-2 years, and excluding non-epileptic events and poor compliance (Beleza, 2009).

Epidemiologic studies suggest three different patterns of drug resistance in epilepsy: de novo, progressive, and waxing-and-waning.

**De novo drug resistance**

In some patients, resistance is present from the time of onset of the very first seizure, before any antiepileptic drug is
even started. One landmark study showed that patients with newly diagnosed epilepsy for whom the first drug was ineffective had only an 11% probability of future success, compared with 41% to 55% in patients who had had to stop taking the drug because of intolerable side effects or idiosyncratic reactions. Most patients for whom the first drug fails will be resistant to most and often all antiepileptic drugs (Kwan and Brodie, 2000).

**Progressive drug resistance**

In some patients, epilepsy is initially controlled but then gradually becomes refractory. This pattern may be seen, for example, in childhood epilepsies or in patients with hippocampal sclerosis (Berg et al., 2006).

**Waxing and waning resistance**

In some patients, epilepsy has a waxing and waning pattern: i.e., it alternates between a remitting (pharmacoresponsive) and relapsing (pharmacoresistant) course. Patients thought to have drug-resistant epilepsy may become seizure-free when other drugs are tried. Changes in drug bioavailability, local concentration of the drug in the brain, receptor changes, the development of tolerance, and interactions with new medications may be implicated, though the exact mechanism is not understood (Loscher and Schmidt, 2006).
Conceptually, the variable response to antiepileptic drugs can be attributed to factors related to the disease, the patient, and the drugs, or to other unknown factors. These factors are not mutually exclusive and may be either constitutive or acquired during the course of the disease.

- **Factors related to the disease**: These factors include etiology, epilepsy progression resulting in persistent changes of the epileptogenic network, and alterations of drug targets or drug uptake into the brain.

- **Factors related to the drugs**: Several drug-related factors have been implicated, such as the development of tolerance, lack of antiepileptogenic (disease-modifying) actions to interrupt the ongoing process of epileptogenesis rather than only suppressing seizures, and paucity of drugs with specific mechanisms of action tailored to difficult-to-control epilepsies.

- **Patient characteristics**: Variability in response (efficacy and adverse effects) to each antiepileptic drug can be due to interindividual differences in any of four interrelated fundamental factors: DNA, RNA, proteins, or metabolites. Age-related changes in pharmacokinetic and pharmacodynamic variables may contribute to age-dependent pharmacoresistance. Least studied are environmental factors that may play a role in the development or expression of pharmacoresistance *(Pati and Alexopoulos, 2010).*
In epilepsy, 3 prognostic groups are generally considered: (1) spontaneous remission (20–30%) as seen in benign epilepsy with centrotemporal spikes or childhood absences; (2) remission on Anti-epileptic drugs (20–30%) as occurs in most focal epilepsy and myoclonic juvenile epilepsy syndromes; (3) persistent seizures under Anti-epileptic drugs (30–40%) among which refractory epilepsy is included (Kwan and Sander, 2004).

The pathogenesis of refractoriness is multifactorial and variable and could include genetic and environmental factors. The underlying syndrome or causative pathology is a major factor in determining drug response. Certain structural abnormalities, such as hippocampal sclerosis, appear to be particularly pharmaco-resistant. At the molecular level, changes in the neuronal network and the composition or functioning of neurotransmitter receptors also may play a role (Kwan and Brodie, 2005).

A younger age at onset of epilepsy predicts refractoriness. Seizures in the immature brain of a child may result in nonpruning of neurons and contribute to high numbers of gap junctions, which leads to abnormal connectivity, the hyper connected cortex (Ko and Holmes, 1999).
High seizure frequency (more than 1 seizure per month) occurring soon after the diagnosis of epilepsy either before or after treatment onset correlates with refractoriness in the short term (2–4 years) and long term (30–35 years) (Berg et al., 2001).

In focal epilepsy, hippocampal sclerosis, cortical dysplasia and hemorrhage are associated with refractoriness. Depression has recently also been associated with lack of response to Anti-epileptic drugs. Neurobiological processes that underpin depression may interact with those producing seizures to increase the extent of brain dysfunction and thereby the likelihood of developing pharmaco-resistant epilepsy (Hitiris et al., 2007).

Electroencephalography is useful for predicting refractoriness. The quantity of interictal spikes is predictive of severity in temporal lobe epilepsy. Oligospiers, patients with temporal lobe epilepsy with less than 1 spike per hour, correlate with less severe epilepsy. In addition, some studies describe the association between multifocal spikes and intractability (beleza 2009).

Factors that have been associated with treatment-resistant epilepsy include:

- Early onset of seizures
• Long history of poor seizure control
• Having more than one type of seizure
• Remote symptomatic etiology (eg, patients with a history of brain infection or head trauma)
  • Certain structural abnormalities (eg, cortical dysplasia)
  • Certain abnormalities on electroencephalography (EEG)
  • Cognitive disability
  • History of status epilepticus

(Pati and Alexopoulos, 2010)
PHARMACORESISTANCE

Transporter hypothesis
- P-glycoprotein as a member of a transporter superfamily
- Substrates and inhibitors of p-glycoprotein
- Other efflux transporters in the brain
- Cerebral expression of p-glycoprotein
- Control of p-glycoprotein expression
- Mechanisms of over-expression
- Are antiepileptic drugs substrates of drug transporters?

Target hypothesis
- Voltage-gated Na+ channels
- Other types of voltage-gated channels
- Neurotransmitter systems: GABA
- Genetic control of anti-epileptic drug targets
In human epilepsy, one of the most common neurological diseases, the development of resistance to anticonvulsant therapy is a crucial clinical problem, but the mechanisms of drug resistance have remained elusive (Remy et al., 2003a).

In the presence of adequate, carefully monitored serum anti-epileptic drug levels, drugs have to traverse the blood brain barrier. Consequently, one scenario to explain pharmacoresistance could be that sufficient intraparenchymal anti-epileptic drug concentrations are not attained, even in the presence of adequate anti-epileptic drug serum levels. Such a phenomenon could arise via an enhanced function of multidrug transporters that control intraparenchymal anti-epileptic drug concentrations. Following permeation into the CNS parenchyma, drugs have to bind to one or more target molecules to exert their desired action. Thus, pharmacoresistance may also be caused by a modification of one or more drug target molecules. These modifications would then cause a reduced efficacy of a given anti-epileptic drug at the target (Remy and Beck, 2006).

Consequently, two main hypotheses have been proposed to account for Pharmacoresistant epilepsy.

The first hypothesis contends that pharmaco-resistance arises because Anti-epileptic drugs do not gain access to their sites of action in the brain. This phenomenon is thought to be
caused by over-expression of drug efflux transporters at the blood brain barrier that limit anti-epileptic drug access to the brain. Furthermore, this can also occur in glial and neuronal membranes, potentially reducing drug efficacy by restricting access to intracellular target sites. Because of the central importance of multidrug transporters, this hypothesis has been designated “transporter hypothesis”.

The target hypothesis, on the other hand, contends that target receptor sites are somehow altered in the epileptic brain so that they are much less sensitive to the anticonvulsant effects of systemically administered drugs (Beck, 2007).

**Transporter hypothesis**

An important characteristic of pharmacoresistant epilepsy is that most patients with refractory epilepsy are resistant to most, and often all, anti-epileptic drugs. As a consequence, patients not controlled on monotherapy with the first anti-epileptic drug have a chance of only about 10% or lower to be controlled by other anti-epileptic drugs, even when using anti-epileptic drugs that act by diverse mechanisms. This point to nonspecific and possibly adaptive mechanisms, such as decreased drug uptake into the brain by seizure-induced over-expression of multidrug transporters in the blood brain barrier (Loscher and Potschka, 2002).
For drugs to enter the brain, they must traverse either blood brain barrier or the blood CSF barrier. Because of these anatomical barriers, entry of drugs into the brain is restricted (Pardridge, 1999).

The restrictive nature of the brain microvessel endothelial cells that form the blood brain barrier is due in part to the formation of tight junctions between the cells and to the lack of transendothelial pathways such as transcellular channels or fenestrations. Consequently, brain capillaries restrict the penetration of hydrophilic, polar, large, or protein-bound compounds, whereas nonpolar, highly lipid-soluble drugs penetrate easily through the blood brain barrier by passive diffusion. With respect to the blood CSF barrier, for a drug to enter the CSF it must pass through the choroid plexus. Because capillary endothelial cells of the choroid plexus are fenestrated and lack tight junctions, the permeation barrier within the choroid plexus exists at the level of the epithelial cells lining the surface. These epithelial cells are mainly joined by tight junctions, which restrict entry of water-soluble molecules (Spector, 2000).

However, apart from passive diffusion, drugs may also enter and leave the brain by carrier-mediated transport processes. In this respect, the recent finding of multidrug transporters of the ATP-binding cassette superfamily, such as
P-glycoprotein (P-gp) and multidrug resistance-associated protein (MRP), in the endothelial cells of the blood brain barrier is of particular interest, since these outwardly directed active efflux mechanisms appear to act as an active defense mechanism, limiting brain accumulation of many lipophilic drugs. Furthermore, both P-gp and MRP are expressed in choroid plexus epithelial cells that form the blood CSF barrier (Loscher and Potschka, 2002).

The primary function of these proteins is to pump lipophilic drugs and other xenobiotics out of cells and thereby prevent the accumulation of potentially toxic substances. In doing so, however, these proteins may also decrease the efficacy of pharmacological agents by limiting their access to target tissues in the brain (Loscher, 2007).

A number of drug transporter genes and their proteins are over-expressed in the blood brain barrier of individuals with refractory epilepsy. This has been demonstrated in tissues taken from epileptic foci at the time of resective surgery. Specific data indicate that there is a 130% increase in the expression of MDR1, the gene encoding for P-gp, a 180% increase in MRP5, and a 225% increase in MRP2 in brain capillary endothelial cells isolated from epileptic individuals in comparison with non-epileptic controls. Additional data indicate that P-gp,
MRP1, and MRP2 are also over-expressed in glial and/or neuronal cells of patients with intractable epilepsy (Dombrowski et al., 2001).

Based on the assumption that penetration of drugs from blood into brain and CSF depends mainly on the drugs’ lipid solubility, drugs required to act within the brain, such as antiepileptic drugs, have generally been made lipophilic. Anti-epileptic drugs penetrate into the CSF by simple diffusion and lipid solubility plays the major role in determining the difference in rate of entry of anti-epileptic drugs into the brain. However, one anti-epileptic drug, valproate, did not fit into this scheme. Valproate is almost completely ionized at physiologic PH. However, valproate penetrated into the CSF and brain very rapidly. Indeed, valproate was the first anti-epileptic drug for which an active transport in the blood CSF barrier and blood brain barrier has been proposed (Loscher and Potschka, 2002).

P-glycoprotein as a member of a transporter superfamily

P-gp is believed to confer the multidrug resistance phenotype by reducing intracellular drug accumulation through its function as an active efflux pump. It belongs to a highly conserved protein superfamily, the ATP-binding cassette
proteins, which has more than 100 members and can be found in all kinds of organisms (Kwan and Brodie, 2005).

With few exceptions, they function as active pumps at the cell membrane through hydrolysis of ATP to drive the flux of their substrates against the concentration gradient. The substrate range for these proteins is diverse and includes drugs, nutrients, amino acids, sugars, peptides, pigments, and metals (Silverman, 1999).

At least 48 human ATP-binding cassette (ABC) genes have been identified and grouped under subfamilies ABCA (ABC1), ABCB (MDR/TAP), ABCC (MRP/CFTR), ABCD (ALD), ABCE (OABP) and ABCF (GCN20), and ABCG (White) (Dean et al., 2001).

P-gp is encoded by a small gene family, comprising two genes in humans, designated MDR1 (systematic name ABCB1) and MDR2 (ABCB4), located near each other on chromosome 7q21.1. It is encoded by three genes in rodents, mdr1a, mdr1b, and mdr2. Human MDR1 and rodent mdr1a and 1b encode the drug transporter associated with multidrug resistance, whereas MDR2 and mdr2 do not confer the multidrug-resistance phenotype. The rodent mdr1a and mdr1b together are believed to cover the same tissue distribution and function as the single human MDR1 P-gp (Kwan and Brodie, 2005).
Human P-gp is an integral membrane protein with 1,280 amino acids. Similar to other ATP-binding cassette transporters, P-gp comprises two homologous halves, each consisting of one transmembrane domain containing six segments, and one nucleotide-binding domain or ATP-binding cassette unit. The exact three-dimensional structure and mechanism of action of P-gp are still unclear (McKeegan et al., 2003).

**Fig. (1)** Typical structure of the ATP-binding cassette transporters (Lazarowski et al., 2007).

### Substrates and inhibitors of p-glycoprotein

Unlike most energy-dependent pumps, P-gp is highly promiscuous. Hundreds of structurally and chemically unrelated compounds, as diverse as anthracyclines (doxorubicin), alkaloids (vincristine), specific peptides (cyclosporine A), steroid hormones (hydrocortisone), local anesthetics (dibucaine), and dye molecules (rhodamine 123), have been identified as substrates. How P-gp recognizes such a diverse
range of compounds is largely unexplained (Kwan and Brodie, 2005).

Ever since the role of P-gp was recognized in drug resistance, inhibitors to circumvent its functions have been sought. This has yielded another long list of compounds that increase the sensitivity of cells in vitro to cytotoxic substrate drugs. The mechanisms of action of these inhibitors or modulators are largely unknown, but many of them are substrates for P-gp, suggesting that they act by competitive inhibition (Avendano and Menendez, 2002).

Table (1) P-gp substrates (Kwan and Brodie, 2005).

<table>
<thead>
<tr>
<th>Anticancer drugs</th>
<th>Other cytotoxic agents</th>
<th>Steroids</th>
<th>Miscellaneous</th>
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<tr>
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<td>Aldosterone</td>
<td>Digoxin</td>
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<td>Daunorubicin</td>
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<td>Dexamethasone</td>
<td>Protease inhibitors</td>
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<td>Loperamide</td>
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<td>Rhodamine 123</td>
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<td>Etoposide</td>
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<td>99mTc-SESTAMIBI</td>
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<td>Teniposide</td>
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<td>Actinomycin D</td>
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<td>Mitoxantrone</td>
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<td>Peptides</td>
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<td>Leupeptin</td>
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<td>Pepstatin A</td>
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<td>Gramicidin D</td>
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<td>Nonactin</td>
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Table (2) P-gp inhibitors (Kwan and Brodie, 2005).

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<tr>
<th>Calcium channel blockers</th>
<th>Cyclic peptides</th>
<th>Phenothiazines</th>
<th>Steroids</th>
<th>Antibiotics</th>
<th>Miscellaneous</th>
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<td>Progesterone</td>
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<td>Chlorpromazine</td>
<td>Tamoxifen</td>
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<td>Cortisol</td>
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<td>Nicardipine</td>
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<td>Propranolol</td>
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25
Other efflux transporters in the brain

Assessing the role of P-gp in drug resistance of CNS disorders such as epilepsy is further complicated by the presence of other efflux transporters in the brain, which are relatively less well characterized. Among them, the best studied is the multidrug resistance protein [MRP, also called multidrug resistance-related or -associated protein] family with at least nine members identified in humans (Borst et al, 2000).

Although also capable of conferring multidrug resistance, MRPs differ from (and overlap with) P-gp in substrate specificity, structure, tissue distribution, and possible physiologic functions (Seelig et al., 2000).

With respect to the role of MRPs in blood brain barrier function, differences in the cellular location of MRPs have to be considered. Whereas MRP2 is located in apical cell membranes, which is the appropriate position for a protective role, other MRPs, including MRP1, MRP3, and MRP5, are located basolaterally, so that over-expression of the latter MRPs in brain capillary endothelial cells would not reduce entry of drugs into the brain (Dombrowski et al., 2001).
MRP2

Using cDNA arrays, a 225% increase in MRP2 gene expression was found in brain capillary endothelial cells from patients with drug resistant temporal lobe epilepsy (TLE), suggesting that MRP2 expression changes may play an important role in resistance to anti-epileptic drugs by decreasing the permeability of anti-epileptic drugs across the blood brain barrier (Dombrowski et al., 2001).

Both inhibition of MRP2 and lack of MRP2 result in a significant increase of drug levels in the brain. The localization of MRP2 to the luminal surface of the brain capillary endothelium, and the wide spectrum of drugs accepted as substrates by MRP2 implicate that this transporter may be as important as P-gp in blood brain barrier function. MRP2 and P-gp have an overlapping substrate spectrum which is known from substrate recognition studies on P-gp and MRPs (Loscher and Potschka, 2002).

In addition to the MRP2 gene, the genes encoding for MRP3 and MRP5 were found to be significantly over-expressed in patients with refractory epilepsy, whereas expression of the MRP1 gene was not significantly altered. Of these MRP genes, the largest over-expression in brain capillary endothelial cells was seen for the MRP2 gene (Dombrowski et al., 2001).
Cerebral expression of p-glycoprotein

P-gp is expressed on the apical side of the choroid plexus epithelia, contributing to the blood CSF barrier. At the blood brain barrier level, ongoing debate exists as to the precise subcellular localization (luminal vs. antiluminal) of P-gp in the cerebral capillary endothelial cells. Most of the published studies do suggest that P-gp is principally expressed at the luminal (apical) membrane of the capillary endothelial cells in the brain. However, some authors have localized P-gp to neighboring astrocytic foot processes on the antiluminal (basolateral) side of brain microvasculature. Expression of P-gp at locations other than the apical membrane of capillary endothelium suggests that the function of P-gp may extend beyond the blood brain barrier (Kwan and Brodie, 2005).

Yet, there is some evidence that under pathological conditions, such as epilepsy, P-gp in astrocyte foot processes may be involved in blood brain barrier function. In the rodent brain, the mdr1a P-gp isoform is predominantly expressed in brain microvessel endothelial cells of the blood brain barrier, whereas the mdr1b P-gp isoform is preferentially expressed in astrocytes (Declèves et al., 2000).

In the normal human brain, P-gp is highly expressed in capillary endothelial cells, but cannot be detected by routine
immunohistochemistry in brain parenchyma, i.e., astrocytes or neurons. One explanation for the apparent difference in astrocytic P-gp expression could be that P-gp in normal human astrocytes is below the detection level of the assays used, because under pathological conditions, such as epilepsy, P-gp becomes detectable in human astrocytes (Sisodiya et al., 2002).

**Control of p-glycoprotein expression**

**A-Genetic control**

The nature of ATP-binding cassette transporter genes indicates that their expression can be induced in previously non-expressive cells. Consequently, over-expression of these proteins could be observed in blood brain barrier-related cells and brain parenchyma cells, including neurons from clinical end experimental studies (Lazarowski et al., 2007).

_Tishler et al. (1995)_ were the first to report that brain expression of _MDR1_ gene, which encodes the multidrug transporter P-gp in humans, is markedly increased in the majority of patients with medically intractable partial (mostly temporal lobe) epilepsy. In line with enhanced _MDR1_ expression in epileptogenic brain tissue, immunohistochemistry for P-gp showed increased staining in capillary endothelium and astrocytes.
By using gene arrays to study mRNAs of multidrug transporters in endothelial cells isolated from surgically resected epileptic foci of patients with pharmacoresistant partial epilepsy, Janigro and colleagues’ determined increased expression of \textit{MDRI} and the gene encoding MRP2, indicating that over-expression of both P-gp and MRP2 in the blood brain barrier may be involved in resistance to anti-epileptic drugs (\textit{Dombrowski et al., 2001}).

\textit{MDRI} is highly polymorphic. Sequence analyses covering the entire gene in 24 healthy white volunteers identified 15 mutations, with a relatively common polymorphism, C3435T in exon 26. \textit{MDRI} 3435 TT genotype was associated with lower P-gp expression in enterocytes than those with CT or CC genotypes. Subjects with CC genotype were found to have higher P-gp function than those with TT genotype (\textit{Hoffmeyer et al., 2000}).

Considerable ethnic variation is found in the frequency of the \textit{MDRI} C3435T genotype, such that 65% to 83% of African blacks express the TT genotype, but only around 25% of white people do so, with the frequencies among Asians lying somewhere in between (\textit{Ameyaw et al., 2001}).

\textbf{B-Environmental control}

Expression of P-gp is highly inducible by environmental factors. \textit{MDRI} expression has been found to be induced by heat
shock, arsenite, partial hepatectomy, growth factors, sodium butyrate, protein kinase C agonists, and even its substrates and inhibitors (Kwan and Brodie, 2005).

Mechanisms of over-expression

An important question is whether the over-expression of efflux transporters in epileptic brain tissue is constitutive or acquired/induced, or both mechanisms may be at play. A constitutive over-expression could occur as a result of genetic predisposition, or it could be intrinsic to the development of the specific pathology. It also is conceivable that over-expression is acquired, such as induction by recurrent seizures or even the anti-epileptic drugs intended to prevent them. Current preliminary evidence suggests that both situations could be taking place (Kwan and Brodie, 2005).

- Acquired (induced) over-expression

An open question is whether the over-expression of P-gp and MRPs in epileptogenic brain tissue of patients with pharmacoresistant epilepsy is a consequence of epilepsy, uncontrolled seizures, and chronic treatment with anti-epileptic drugs, or combinations of these factors. Because pharmacoresistant patients have the same extent of neurotoxic side effects under anti-epileptic drug treatment as patients who are controlled by anti-epileptic drugs, the over-expression of
drug transporters in pharmacoresistant patients is most likely restricted to the epileptic focus or circuit (Loscher and Potschka, 2002).

This is substantiated by the finding that over-expression of P-gp and MRP1 was found in epileptogenic tissue but not adjacent normal tissue. In this respect, it is also interesting to note that in patients in whom the epileptic focus has been resected during epilepsy surgery -resulting in seizure control under treatment with anti-epileptic drugs - seizures may recur after cessation of anti-epileptic drug treatment and become pharmacoresistant again, suggesting that a “secondary focus” has become activated and drug-resistant (Sisodiya et al., 2002).

For ethical and methodologic reasons, it is difficult to conduct longitudinal studies to examine the possibility of induction of transporters by epileptogenesis, seizures, or anti-epileptic drug treatment in humans. Most data in this regard have come from animal studies (Kwan and Brodie, 2005).

Using monoclonal antibody staining, there was observed regional-specific over-expression of P-gp in the hilus of the dentate gyrus and CA3 region of the hippocampus in rats 1 week after pilocarpine-induced status epilepticus. Most importantly, there was no comparable staining of hippocampal
neurons in non-seizing controls, indicating that the upregulation of P-gp was a consequence of the experimentally induced seizure activity (Loscher, 2007).

Results observed in some experiments indicated that MDR1 over-expression depends on the seizure-stress frequency. Also, this expression exhibits a selective sequential pattern in term of the type of cells affected: as the frequency of the induced-seizures increased, more cells, that is, endothelial cells, astrocytes, and surrounding neurons, became MDR-1 positive (Lazarowski et al., 2007).

In rats, kainate-induced seizures have been found to transiently over-express P-gp in astroglia and, less marked, capillary endothelial cells in the hippocampus, indicating that seizures rather than epilepsy are responsible for over-expression of drug transporters. This could explain that one of the major predictors of pharmacoresistance is high seizure frequency prior to initiation of treatment (Zhang et al., 1999).

- **Constitutive over-expression**
  Over-expression of efflux transporters may be constitutive or intrinsic to the lesion itself. This is supported by the observation that in the case of malformations of cortical development, P-gp was upregulated in postmortem archival
tissues from patients who had died before experiencing seizures or exposure to anti-epileptic drugs (*Kwan and Brodie, 2005*).

Furthermore, when determining P-gp and MRP1 expression in three common causes of refractory epilepsy, namely dysembryoplastic neuroepithelial tumors, focal cortical dysplasia, and hippocampal sclerosis, and comparing the expression in the abnormal epileptogenic tissue with P-gp and MRP1 expression in histologically normal adjacent tissue, there was over-expression of both P-gp and MRP1 in reactive astrocytes in the epileptogenic tissue in all three conditions, and MRP1 over-expression in dysplastic neurons in focal cortical dysplasia (*Sisodiya et al., 2002*).

Increased expression of P-gp, as well as MRP, has been associated with refractory epilepsy in tuberous sclerosis. Increased levels of P-gp were found in astrocytes and blood vessel endothelium in hippocampal samples obtained from patients with refractory mesial temporal lobe epilepsy compared with control samples (*Robey et al., 2008*).

- **Other mechanisms**
  
  In addition to intrinsic or acquired over-expression of multidrug transporters in the blood brain barrier or blood CSF barrier of patients with epilepsy, functional polymorphisms of
these transporters may play a role in pharmacoresistance (*Kerb et al., 2001*).

Furthermore, over-expression and functional polymorphisms of multidrug transporters in patients with pharmacoresistant epilepsy need not necessarily be restricted to the brain, but could also occur in other tissues, such as the small intestine, where P-gp is thought to form a barrier against entrance of drugs from the intestinal lumen into the bloodstream, thereby limiting their oral bioavailability (*Loscher and Potschka, 2002*).

In view of data indicating that the endothelial barrier function of the blood brain barrier is transiently disrupted during seizures, over-expression of multidrug transporters in glial endfeet covering the blood vessels may represent a “second barrier” under these conditions (*Loscher and Potschka, 2002*).

Over-expressed multidrug transporters lower the extracellular concentration of anti-epileptic drugs in the vicinity of the epileptogenic pathology and thereby render the epilepsy caused by these pathologies resistant to anti-epileptic drug treatment (*Sisodiya et al., 2002*).

P-gp over-expression can be induced locally by microinjection of glutamate. Intracerebral microinjections of
glutamate at nanomolar levels were sufficient to locally increase P-gp expression without seizure activity. P-gp expression in more distal regions of the brain was not significantly affected. These particular data suggest that molecular factors inducing P-gp over-expression in the blood brain barrier, even in the absence of seizures, could precondition the refractory phenotype for some epileptic syndromes (Bauer et al., 2008).

**Are antiepileptic drugs substrates of drug transporters?**

According to the drug transporter hypothesis, the expression of drug efflux transporters in the brain capillaries of normal brain should not restrict the penetration of anti-epileptic drugs to any significant extent. However, in epileptic brain, where multidrug transporters are over-expressed in brain capillaries as well as in the astrocytic foot processes surrounding these capillaries, brain penetration of anti-epileptic drugs should be reduced in a regional-specific fashion. Moreover, over-expression of drug efflux transporters in neurons and glia of the brain parenchyma would further limit the effectiveness of anti-epileptic drugs by restricting access to intracellular target sites. To verify this hypothesis, it first needs to be determined if anti-epileptic drugs are substrates for
multidrug transporters in the blood brain barrier. Recent data from multiple laboratories support this claim (Loscher, 2007).

Indeed, there is increasing evidence that various major anti-epileptic drugs are substrates for one or more of these efflux carriers. At least three strategies are used in this respect. One is to evaluate whether the brain penetration of anti-epileptic drugs can be affected by P-gp or MRP inhibitors; a second is to use cell lines that over-express P-gp or MRPs; and a third is to study drug penetration into the brain of mdr or mrp knockout mice (Potschka et al., 2001).

The only P-gp inhibitors that have been clinically evaluated in combination with anti-epileptic drugs in patients with epilepsy are calcium channel blockers such as verapamil, nifedipine, or diltiazem. Verapamil and diltiazem increased the plasma concentrations of carbamazepine (probably by inhibiting its CYP3A4-mediated metabolism) and caused unacceptable neurotoxicity, but encouraging clinical observations were reported for add-on treatment with nifedipine in patients with refractory partial seizures (Loscher and Schmidt, 1994).

However, because calcium channel antagonists exert anticonvulsant activity of their own and inhibit CYP3A4, it is not possible to judge whether the favorable effect of
combinations of nifedipine and anti-epileptic drugs was due to inhibition of P-gp, inhibition of CYP3A4, or blockade of calcium channels (Loscher and Potschka, 2002).

Using microdialysis in freely moving rats, it was found that brain penetration of systemically administered phenytoin nearly doubled 0.5-1.5 hours after a unilateral intracerebral injection of the P-gp transport inhibitor, verapamil, in comparison with the contralateral, noninjected hemisphere (Potschka and Loscher, 2001).

Similarly, phenytoin brain concentrations are significantly increased in mdr1 knockout mice that lack the gene encoding for P-gp in comparison with wild-type controls. Conversely, over-expression of P-gp, produced as a result of kainate-induced status epilepticus, significantly decreases the blood brain barrier permeability of phenytoin in the hippocampus in comparison with non-epileptic control rats (Rizzi et al., 2002).

Taken together, these results demonstrate that the multidrug transporter, P-gp, regulates phenytoin entry into the brain.

Additional data have shown that a number of other anti-epileptic drugs, including carbamazepine, mild malformation of cortical development, lamotrigine, gabapentin, and topiramate, are also substrates for P-gp, MRPs, or both. Hence, it appears
that an over-expression of P-gp could potentially affect the efficacy of a variety of different anti-epileptic drugs (Loscher and Potschka, 2005).

Absence of MRP2 in the blood brain barrier led to increased penetration of phenytoin into the brain and significantly enhanced anticonvulsant activity compared with rats with intact MRP2 function. Similar results were obtained when phenytoin was combined with probenecid to inhibit MRP2. Significant increase of drug penetration into the brain by probenecid has previously been reported for the major anti-epileptic drugs valproate and carbamazepine and has been attributed to inhibition of MRP2 in the blood brain barrier (Loscher and Potschka, 2002).

In contrast to phenytoin, phenobarbital’s brain distribution or anticonvulsant activity were not affected by probenecid or lack of MRP2 in the blood brain barrier, indicating that not all anti-epileptic drugs are substrates for this transporter. However, Phenobarbital is a substrate for P-gp so that both MRP2 and P-gp act in concert to restrict the brain penetration of anti-epileptic drugs (Dombrowski et al., 2001).

More recent animal studies revealed that the bidirectional movement of valproate across the blood brain barrier (and possibly also blood CSF barrier) is mediated jointly by passive
diffusion and carrier-mediated transport. The uptake of valproate from blood to brain is facilitated by a medium-chain fatty acid transporter, which accounts for two-thirds of the barrier permeability, whereas the mechanisms governing the efflux of valproate from the brain involve a probenecid-sensitive, active transport system at the brain capillary endothelium (Shen, 1999).

Valproate was the first anti-epileptic drug for which blood CSF barrier and blood brain barrier transport by a probenecid sensitive carrier, most likely MRP, has been reported (Potschka et al., 2001).

Valproate is a substrate for MRPs in brain capillary endothelial cells, which raises the possibility that MRPs may serve as the efflux transporters of valproate and explains the previously described effects of probenecid on brain and CSF levels of valproate, because probenecid is an inhibitor of MRP1 and MRP2 (Borst et al., 2000).

In mdr1 knockout mice, the brain/plasma concentration ratio for carbamazepine was found to be significantly higher in knockout mice than in wild-type controls. Furthermore, significant increases in brain levels were found for topiramate, lamotrigine, and gabapentin in mdr1 knockout mice, although no significant differences to controls were seen for
phenobarbital, phenytoin, valproate, and vigabatrin (*Sills and Kwan, 2001*).

However, use of knockout mice is limited in the study of drug resistance because of the redundancy of the transporters: another transport protein may take over the function of one that has been knocked out (*Schinkel, 1999*).

With respect to the use of cell lines to study anti-epileptic drug transport, it was found that intracellular phenytoin levels in a *MDR1*-expressing neuroectodermal cell line were only one-fourth that in *MDR1*-negative cells, suggesting that P-gp significantly contributes to cell export of phenytoin (*Tishler et al., 1995*).

In human colon carcinoma cells, phenobarbital and, to a much lesser extent, phenytoin were found to up-regulate P-gp, a phenomenon described for several substrates of P-gp (*Schuetz et al., 1996*).

Even though findings appear to support a role for multidrug transporters in pharmacoresistant epilepsy, there are a number of conceptual questions that remain enigmatic. Firstly, epileptic seizures are known to result in a disruption of the blood brain barrier, which would be expected to result in better access of anti-epileptic drugs to brain parenchyma despite the upregulation of multidrug transporters. Secondly, patients are in
many cases treated with anti-epileptic drugs until CNS side effects develop. This seems to indicate that relevant CNS concentrations of anti-epileptic drugs are reached despite transporter upregulation, yet, these patients are resistant to treatment. This apparent discrepancy could potentially arise via local upregulation of drug transporters that only affects anti-epileptic drug concentrations at the epileptic focus (Remy and Beck, 2006).

**Target hypothesis**

It is widely accepted that the efficacy of an anti-epileptic drug is determined by its ability to cross blood brain barrier and bind to intraparenchymal target sites. According to the target hypothesis, pharmacoresistance occurs when target sites are structurally and/or functionally modified in such a way that they become less sensitive to anti-epileptic drugs (Beck, 2007).

This means that molecular drug targets may undergo a genetic or functional modification after which they are no longer sensitive to their ligands (Remy et al., 2003a).

In general terms, a drug target is defined as one that produces a clinically relevant response to a therapeutic dose of a drug, in this case an anti-epileptic drug. A particularly well-investigated drug target of many first-line anticonvulsants is the voltage-gated Na+ channel. A large number of targets for anti-
epileptic drugs have been identified in the brain, many of which undergo molecular changes during chronic epilepsy. So far, a reduced sensitivity of drug targets to anti-epileptic drugs in chronic human epilepsy has been suggested for the voltage-gated Na+ channel and the GABA<sub>A</sub> receptor (Beck, 2007).

Based on the specific targets involved in anti-epileptic drug mechanisms, anti-epileptic drugs can be divided mechanistically into drugs acting by (a) modulation of voltage-gated ion channels (including sodium, calcium, and potassium channels); (b) enhancement of synaptic inhibition [e.g., by potentiating inhibition mediated by γ-aminobutyric acid (GABA)]; and (c) inhibition of synaptic excitation (e.g., by blockade of glutamate receptors). The fact that several anti-epileptic drugs act by more than one of these mechanisms is thought to explain their broad spectrum of clinical efficacy (Schmidt and Loscher, 2005).

Loss of anti-epileptic drug-sensitivity is less pronounced in CA1 neurons than in dentate granule neurons in experimental epilepsy. Thus, these results suggest that target mechanisms of drug resistance are cell type and anti-epileptic drug specific (Schaub et al., 2007).
Voltage-gated Na+ channels

Voltage gated Na+ channels are composed of one of several different pore-forming α subunits that form a complex with additional accessory subunits. They are closed at resting membrane potential but open rapidly upon depolarization. The resultant Na+ inward currents subsequently decrease rapidly toward baseline levels as the Na+ channels undergo inactivation during prolonged depolarization. After inactivation, Na+ channels require hyperpolarization to return to the resting state. The transition between these functional states is rapid and occurs on a time scale of milliseconds, enabling Na+ channels to sustain fast action potentials (Remy et al., 2003a).

The target hypothesis is based primarily on studies with carbamazepine on voltage-gated sodium channels in hippocampal neurons. The primary mechanism of this major anti-epileptic drug is well established and thought to be related to its action on voltage-gated Na+ channels (Remy et al., 2003b).

Carbamazepine is known to inhibit voltage-dependent Na+ currents via two classes of mechanisms. It modestly blocks Na+ channels in their resting state at hyperpolarized membrane potentials, but the blocking effects are enhanced when the resting membrane potential is depolarized. In addition to voltage dependent block, carbamazepine inhibits Na+ currents in an activity- or use-dependent manner; that is, blocking
effects are more pronounced when the cell membrane is repetitively depolarized at high frequencies. Use- and voltage-dependent block of Na\(^+\) channels by carbamazepine generally is assumed to result from preferential binding of these drugs to the inactivated state of the channel (Remy et al., 2003a).

In epileptic brain tissue, use dependent block of Na\(^+\) channel activity is absent. Similar findings have been observed in human brain tissue obtained from carbamazepine -responsive and carbamazepine -resistant patients. In carbamazepine -responsive patients, use-dependent blockade of Na\(^+\) channel activity is observed. In contrast, use-dependent effects are absent in carbamazepine-resistant patients. Taken together, these findings suggest that a clinical loss of carbamazepine efficacy in epilepsy patients is associated with a reduction in the drug sensitivity of Na\(^+\) channels in the brain (Beck, 2007).

In CA1 neurons, the effects of carbamazepine on the steady-state inactivation properties of inward Na\(^+\) current were transiently reduced in the kindling model of epilepsy. In contrast to these comparatively modest and transient effects, a complete and long-lasting loss of use-dependent blocking effects of carbamazepine was found in the pilocarpine model of epilepsy in hippocampal dentate granule cells, as well as in epilepsy patients with carbamazepine-resistant temporal lobe epilepsy (Remy et al., 2003a).
This dramatic loss of a major mechanism of action of carbamazepine did not extend to other anti-epileptic drugs known to affect inward Na\(^+\) current. Following pilocarpine induced status epilepticus; the use-dependent effects of phenytoin were reduced, but not completely lost, while the effects of lamotrigine were completely unchanged. It is at present unclear why use-dependent block by carbamazepine and phenytoin is lost or reduced, whereas use dependent block by lamotrigine remains intact in experimental epilepsy. This is an intriguing question because it has been suggested that all three drugs bind to the same site on Na\(^+\) channels (Remy and Beck, 2006).

What mechanisms can account for an altered sensitivity of Na\(^+\) channels in epileptic tissue? One possibility may be that the subunit composition of these channels is altered, such that the expression of anti-epileptic drug-insensitive subunits or subunit combinations is promoted. Indeed, numerous changes in Na\(^+\) channel subunit expression have been observed in both human and experimental epilepsy. In this respect, the downregulation of accessory Na\(^+\) channel β1 and β2 subunits following experimentally induced status epilepticus appears to be a consistent finding (Ellerkmann et al., 2003).
Other types of voltage-gated channels

Ca\(^{2+}\) channels can be subdivided into two groups: high threshold Ca\(^{2+}\) currents and a group of low threshold currents (also termed T-type Ca\(^{2+}\) currents). T-type channels are critically important in controlling the excitability of the postsynaptic compartment of neurons, both in normal and epileptic neurons. A number of anti-epileptic drugs has been shown to inhibit high threshold Ca\(^{2+}\) channels in native neurons at high therapeutic concentrations. Some anti-epileptic drugs potently inhibit low threshold T-type Ca\(^{2+}\) channels, which are not expressed presynaptically. The effects of anti-epileptic drugs on the T-type Ca\(^{2+}\) channel subunits, as well as in native neurons, are diverse (Remy and Beck, 2006).

Neurotransmitter systems: GABA

GABA is the predominant inhibitory neurotransmitter in the adult brain and plays a critical role in the regulation of excitability of neuronal networks (Mody and Pearce, 2004).

GABA binding to GABA\(_A\) receptors causes opening of the receptor which is permeable to Cl\(^-\) and to a lesser extent to HCO\(_3\). In the presence of a normal adult transmembraneous Cl\(^-\) gradient, this results in expression of an inhibitory post-synaptic current that hyperpolarizes the post-synaptic neuronal
membrane. Direct modulators of GABA_A receptors include benzodiazepines and barbiturates. Specifically, GABA receptors on isolated hippocampal neurons from epileptic brain were less responsive to zolpidem, a benzodiazepine site agonist, in comparison to nonepileptic controls. These results suggest that alterations in GABA_A receptor activity may be another target mechanism of pharmacoresistance to certain anticonvulsant drugs (Remy and Beck, 2006).

GABA_A receptors mediate the majority of fast inhibitory neurotransmission in the brain. GABA_A receptors can be assembled from seven distinct subunit families defined by sequence similarity: alpha, beta, gamma, delta, pi, theta, and rho. Most GABA_A receptor subtypes in the brain are believed to be composed of alpha, beta, and gamma subunits. The role of the other subunits, which have a very limited expression pattern in the brain, remains to be determined (Schmidt and Loscher, 2005).

The major GABA_A receptor subtype (60% of all GABA_A receptors) is assembled from the subunits α1β2γ2, with only a few brain regions lacking this receptor. This receptor subtype mediates to a large extent the anticonvulsant action of benzodiazepines, whereas, for instance, α4- or α6-containing subunit assemblies are insensitive to benzodiazepines and other
benzodiazepine site agonists such as zolpidem. Thus any change in the subunit composition of GABA_A receptors can have dramatic consequences for the anticonvulsant efficacy of benzodiazepines and possibly other anti-epileptic drugs that act via the GABA_A receptor (*Schmidt and Loscher, 2005*).

In normal dentate granule cells, GABA_A receptors are insensitive to zinc, which is released from mossy fibers and functions as a negative allosteric modulator of GABA_A receptors. This zinc insensitivity of normal GABA_A receptors is a result of high levels of expression of the α1 subunit in these cells. In epileptic rats, expression of the α1 subunit decreases, and expression of α4 and δ subunits increases, leading to an assembly of GABA_A receptors that are strikingly zinc sensitive. In addition to the enhanced zinc sensitivity, GABA_A receptors from the epileptic hippocampus lose their sensitivity to augmentation by zolpidem (*Coulter, 2000*).

Regarding GABA_A receptor agonists, reduced activity of such substances has been described in a chronic model of epilepsy. In the pilocarpine model of epilepsy, GABA_A receptors of dentate granule cells show a reduced sensitivity to drugs acting on the benzodiazepine receptor site 1 (*Cohen et al., 2003*).
Combined molecular and functional studies indicate that a transcriptionally mediated switch in the alpha subunit composition of GABA<sub>A</sub> receptors occurs in epileptic animals, in particular a decrease of α1 subunits and an increase of α4 subunits. These findings correlate well with the observed changes in benzodiazepine receptor pharmacology (Remy and Beck, 2006).

The specific changes in drug targets described above are an attractive concept to explain pharmacoresistance. It is important to realize, however, that not only changes in drug targets themselves, but also changes in other molecules that affect their function may have important consequences for anti-epileptic drug efficacy. This idea is exemplified by recent findings regarding the role of GABA in epilepsy. GABA may on occasion act as an excitatory neurotransmitter in the immature brain (Remy and Beck, 2006).

A depolarizing action of GABA<sub>A</sub> receptor activation arises because of an altered chloride homeostasis, resulting in a changed chloride gradient across the neuronal membrane. The altered chloride reversal potential then results in a net outward flux of Cl<sup>-</sup> through the GABA<sub>A</sub> receptor ionophore, causing depolarization of the neuron (Mody and Pearce, 2004).
Interestingly, in addition to the developing brain, depolarizing GABA responses appear to be a feature of some neurons in the epileptic brain (Cohen et al., 2002).

Augmenting such depolarizing GABA-mediated potentials by application of GABA agonists is likely to facilitate action potential generation to excitatory input and thereby would increase neuronal excitability instead of decreasing it (Gulledge and Stuart, 2003).

Whether depolarizing GABA responses really play a role in pharmacoresistance to GABA mimetic drugs remains to be seen. These considerations do, however, illustrate the need to consider changes in drug targets within the more general setting of a chronically epileptic brain (Remy and Beck, 2006).

Genetic control of anti-epileptic drug targets

It has become clear over the recent years that seizures cause coordinated and cell-specific transcriptional changes that result in either an up- or down-regulation of families of ion channel mRNAs. This, in turn, causes alterations in the subunit composition or density of ion channels, resulting in altered intrinsic and synaptic neuronal properties (Beck, 2007).
It is important to note that gene polymorphisms relevant for pharmacoresistance may occur both in promoter regions as well as in introns and exons. Gene polymorphisms within the coding regions of such genes would result in a difference in ion channel or transporter proteins that precedes the onset of epilepsy. Polymorphisms in promoter regions, which affect the transcription of such genes, may affect activity-dependent transcriptional regulation of these genes by seizures. This provides a potential mechanism for the acquisition of a pharmacoresistant phenotype during epileptogenesis in pharmacoresistant—as opposed to Pharmacoresponsive-patients (Remy and Beck, 2006).

Firstly, genetic polymorphisms in ion channel drug targets have been identified that are associated with clinical drug response. For instance, a polymorphism in the SCN1A gene seems to correlate with the maximal doses of the anti-epileptic drugs carbamazepine and phenytoin used clinically in individual patients (Tate et al., 2005).

In addition, mutations in the gene encoding the accessory beta subunit of voltage-gated Na⁺ channels are associated with generalized epilepsy with febrile seizures and incorporation of mutated accessory subunits into the channel complex appears to give rise to channels that are less phenytoin sensitive (Schaub et al., 2007).
Are transcriptional regulatory processes the only ones important in seizure-induced plasticity and altered target sensitivity? This appears unlikely, primarily because of experiments performed by Heinemann and colleagues over several years. These researchers have demonstrated in vitro that seizure activity induced by lowering extracellular magnesium levels or blocking potassium channels evolves from an anti-epileptic drug responsive to an anti-epileptic drug resistant form within 30–120 min. This transition is likely too fast to be mediated by a transcriptional change in ion channel expression. Alternatively, ion channel subunits may be modified by redox modulation or phosphorylation, a set of mechanisms that may be invoked much more rapidly than transcriptional changes (Beck, 2007).
GROSS PATHOLOGY

- Malformations of cortical development
  - Focal cortical dysplasia
  - Periventricular nodular heterotopias
  - Tuberous sclerosis complex
  - Glioneuronal tumors

- Do seizures start within the lesion or the perilesional region?

- Is epileptogenesis primarily a result of circuit abnormalities or cellular/molecular defects?

- Expression of drug transporters in pathological lesions associated with refractory epilepsy
Malformations of cortical development

During normal cortical development, immature cortical neurons and glia are primarily generated in the germinal ventricular zone (proliferative stage), although some GABAergic cortical interneurons have also recently been shown to originate from the subcortical ganglionic eminences. While the different stages of cortical development overlap temporally, neurons generated during the proliferative stage proceed to migrate either radially or tangentially to their final location in the cortex (neuronal migration stage) and then develop mature dendrites and axons and form synaptic connections (cortical organization stage) (Wong, 2008).

Malformations of cortical development refer to malformations arising from various aetiologies and presenting with diverse characteristics. In the clinical practice, the classification system of Kuzniecky and Barkovich has gained wide acceptance. According to this classification, malformations of cortical development fall into the following categories: (i) malformations caused by abnormal neuronal and glial proliferation (e.g. hemimegalencephaly, focal cortical dysplasia), (ii) malformations caused by abnormal neuronal migration (e.g. heterotopia, lissencephaly) and (iii) malformations caused by abnormal cortical organization (e.g. polymicrogyria, focal cortical dysplasia without balloon cells) (Kuzniecky and Barkovich, 2001).
Malformations of cortical development are increasingly recognized as causes of epilepsy. The clinical significance and impact of malformations of cortical development are especially high, because malformations of cortical development are frequently associated with pharmaco-resistant epilepsy that is refractory to available seizure medications (Wong, 2008).

Malformations of cortical development are often associated with severe epilepsy and developmental delay. Hemimegalecephaly, an enlarged dysplastic hemisphere, can present as early onset severe epileptic encephalopathy or as partial epilepsy. In focal cortical dysplasia, MRI shows focal cortical thickening and simplified gyration. Tuberous sclerosis (TS) is a multisystemic disorder primarily involving the nervous system; 60% of patients having epilepsy, with 50% having infantile spasms. Bilateral periventricular nodular heterotopia consists of confluent and symmetric nodules of grey matter along the lateral ventricles. X-linked bilateral periventricular nodular heterotopia presents with epilepsy in females and prenatal lethality in most males. Schizencephaly (cleft brain) has a wide anatomo-clinical spectrum, including partial epilepsy in most patients. Polymicrogyria (excessive number of small and prominent convolutions) has a wide spectrum of clinical manifestations ranging from early onset epileptic encephalopathy to selective impairment of cognitive functions (Guerrini et al., 2003).
The histopathological spectrum of malformations of cortical development is large ranging from prominent to only minute changes. Whereas hemimegalencephaly, polymicrogyria, nodular or band heterotopias can be reliably diagnosed in vivo, focal cortical dysplasias often escape imaging techniques (MRI) and may considerably vary in their size and localization (Blumcke et al., 2009).

About 40% of children with drug resistant epilepsy harbour a cortical malformation and up to 50% of the pediatric epilepsy surgery operations are carried out in children with malformations of cortical development (Guerrini et al., 2003).
### Table (3) Classification of cortical malformations *(Barkovich et al., 2001)*

<table>
<thead>
<tr>
<th>Classification</th>
<th>Subclassifications</th>
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</table>
| **I. Malformations due to abnormal neuronal and glial proliferation or apoptosis** | A. Decreased proliferation/increased apoptosis: microcephalies  
1. Microcephaly with normal to thin cortex  
2. Microlissencephaly (extreme microcephaly with thick cortex)  
3. Microcephaly with polymicrogyria/cortical dysplasia  
B. Increased proliferation/decreased apoptosis (normal cell types): megalencephalies  
1. Non-neoplastic  
   a. Cortical hamartomas of tuberous sclerosis  
   b. Cortical dysplasia with balloon cells  
   c. Hemimegalencephaly  
2. Neoplastic (associated with disordered cortex)  
   a. DNT (dysembryoplastic neuroepithelial tumor)  
   b. Gangliogioma  
   c. Gangliocytoma | **II. Malformations due to abnormal neuronal migration**  
A. Lissencephaly/subcortical band heterotopia spectrum  
B. Cobblestone complex  
1. Congenital muscular dystrophy syndromes  
2. Syndromes with no involvement of muscle  
C. Heterotopia  
1. Subependymal (periventricular)  
2. Subcortical (other than band heterotopia)  
3. Marginal glioneuronal | **III. Malformations due to abnormal cortical organization**  
(including late neuronal migration)  
A. Polymicrogyria and schizencephaly  
1. Bilateral polymicrogyria syndromes  
2. Schizencephaly (polymicrogyria with clefts)  
3. Polymicrogyria with other brain malformations or abnormalities  
4. Polymicrogyria or schizencephaly as part of multiple congenital anomaly/mental retardation syndromes  
B. Cortical dysplasia without balloon cells  
C. Microdysgenesis | **IV. Malformations of cortical development, not otherwise classified**  
A. Malformations secondary to inborn errors of metabolism  
1. Mitochondrial and pyruvate metabolic disorders  
2. Peroxisomal disorders  
B. Other unclassified malformations  
1. Sublobar dysplasia  
2. Others |
Focal cortical dysplasia

Focal cortical dysplasia is the single most important cause of focal intractable epilepsy in childhood. It is histopathologically proved in at least 20% of patients in adult epilepsy surgery series and in almost 50% of children undergoing surgical therapy for epilepsy (Luders and Schuele, 2006).

In focal cortical dysplasia, histological abnormalities are restricted to one lobe or to a segment of a few centimeters. Extensive examination of brains with focal lesions may, however, show widespread minor dysplastic changes (Guerrini et al., 2003).

The true prevalence of focal cortical dysplasia in patients with epilepsy is unknown; recent epidemiological studies identified malformations of cortical development in up to 25% of all children with symptomatic epilepsy (Fujiwara and Shigematsu, 2004).

Focal cortical dysplasia as the cause of focal epilepsy can be roughly estimated at 5–10% in developed countries. However, the prevalence of focal cortical dysplasia in focal epilepsy may in fact be lower than 5%, when referring to epilepsy patients on a global basis. In less-developed countries,
infectious diseases such as neurocysticercosis may play a more prominent role in epilepsy aetiology \textit{(Bast et al., 2006)}.

Several classification schemes of cortical malformations have been proposed based on imaging characteristics, genetics, and neuropathology. The histopathological classification systems proposed by Palmini and Luders and Tassi et al. are the two prime systems that are currently used. Palmini and Luders proposed the most frequently used histological classification. It divides focal cortical dysplasia into three major subtypes: mild malformation of cortical development, focal cortical dysplasia type I, and focal cortical dysplasia type II. Two further subcategories are recognized within each of the types: mild malformation of cortical development type I, mild malformation of cortical development type II, focal cortical dysplasia type Ia, focal cortical dysplasia type Ib, focal cortical dysplasia type IIa, and focal cortical dysplasia type IIb \textit{(Krsek et al., 2008)}. 
Table (4) Histopathological classification of focal cortical dysplasia (*Bast et al.*, 2006).

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<th>Palmini and Luders, 2004</th>
<th>Tassi et al., 2002</th>
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<tr>
<td><strong>Mild cortical dysplasia:</strong></td>
<td>Ectopically placed neurons in or adjacent to layer 1 or microscopic neuronal heterotopias outside layer 1.</td>
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<td><strong>Focal cortical dysplasia 1A:</strong></td>
<td>Isolated architectural abnormalities of the cortex.</td>
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<td><strong>Focal cortical dysplasia 1B:</strong></td>
<td>Architectural abnormalities plus giant or immature, but not dysmorphic neurons.</td>
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<td><strong>Focal cortical dysplasia 2A:</strong></td>
<td>Architectural abnormalities with dysmorphic neurones but without balloon cells.</td>
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<tr>
<td><strong>Focal cortical dysplasia 2B:</strong></td>
<td>Architectural abnormalities with dysmorphic neurones and balloon cells.</td>
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<tr>
<td><strong>Architectural dysplasia:</strong></td>
<td>Abnormal cortical lamination and ectopic neurones in white matter.</td>
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<td><strong>Cytoarchitectural dysplasia:</strong></td>
<td>Giant neurofilament-enriched neurones and altered cortical lamination.</td>
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<td><strong>Taylor-type dysplasia:</strong></td>
<td>Giant dysmorphic neurones and balloon cells with laminar disruption.</td>
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Focal cortical dysplasia exhibits a variety of features that in MRI studies are not always all present in combination, nor pathognomonic in isolation: (i) local cortical thickening (often in combination with cortical hyperintensity), (ii) blurring of the grey-matter to white-matter surface, (iii) signal changes in the underlying white matter, usually with an increased signal on T2-weighted images and occasionally with a decreased signal on T1-weighted images (Kuzniecky and Barkovich, 2001).

Fig. (2) MRI of four patients with focal cortical dysplasia. Typical features are (i) focal cortical thickening (patient 1 and 3), (ii) blurring of the grey matter to white-matter surface (patient 1–3), (iii) signal changes in the underlying white matter, usually with an increased signal on T2-weighted images (patient 1–4) (Bast et al., 2006).
Reports from epilepsy surgery programmes may not be used as the gold standard to evaluate MRI sensitivity because of an obvious bias: if no focal cortical dysplasia is detected in MRI, the patient is less likely to be offered an operative therapy than in the case of a focal lesion. Thus, the varying rates of focal cortical dysplasia detected may be attributed to the diverse quality and precision of presurgical MRI investigations (Bast et al., 2006).

Up to 50% of patients with refractory cryptogenic epilepsy (i.e. no MRI lesion) undergoing surgical treatment are shown to have an focal cortical dysplasia: Bautista et al. (2003) reported of a total of 21 patients with normal MRI who underwent resective surgery for intractable epilepsy in Cleveland, OH between 1997 and 2000. In 1/9 temporal and 9/12 extratemporal lobe resections, histopathological findings unmasked an focal cortical dysplasia.

Incomplete myelination may result in negative MRI findings. In infants, where myelination is incomplete, MRI may fail to reveal an focal cortical dysplasia, because of the lack of visual differentiation between white and grey matter (Bast et al., 2006).
Fig. (3) Effect of myelination on MRI sensitivity. Top: Normal T2-weighted MRI of a 7-month-old child suffering from left temporal lobe epilepsy. Bottom: Same patient at 19 months of age. MRI is suspect for focal cortical dysplasia with blurred grey–white matter surface and prolonged T2-signal (Bast et al., 2006).

Focal cortical dysplasia usually presents with intractable partial epilepsy, starting at a variable age, but generally before the end of adolescence. Since lesions may be located anywhere in the brain, any type of focal seizure can be observed and focal status epilepticus has been frequently reported. However, infantile spasms may be the first manifestation (Guerrini et al., 2003).
Epilepsy due to focal cortical dysplasia commonly begins in the first few years of life and may occur shortly after birth. The histopathological type without balloon cells (type 2A) is related to a very early onset compared with focal cortical dysplasia with balloon cells (type 2B). Single cases presented with epilepsy onset after the fourth decade in life in late adulthood (Fauser et al., 2004).

The following epilepsy risk factors were reported in the personal history of 55 patients operated for focal cortical dysplasia: positive family history of epilepsy in 18%, febrile seizures in 16%, status epilepticus in 11%, trauma in 16%, CNS infection in 11% and perinatal complications in 4%. Therefore, one should consider the possibility of an focal cortical dysplasia, even in the presence of other obvious factors of epileptogenesis (Bautista et al., 2003).

In focal cortical dysplasia patients, who have been operated on in early childhood, drawbacks in psychomotor development were observed in up to 70–80% (Francione et al., 2003). It is presumed that the size of lesion, the localization (especially in the case of temporal localization) and even the histopathological subtype play a major role in the manifestation and grade of developmental delay (Lawson et al., 2005).
The term “dual pathology” describes the coincidence of extrahippocampal temporal lesions and Ammon’s horn sclerosis. According to this definition, the majority of associated lesions are malformations of cortical development: Salanova et al. investigated 37 patients operated for dual pathology. Heterotopia and cortical dysplasia were the most common findings. In contrast, over one-third of cases of focal cortical dysplasia are associated with a hippocampal sclerosis. Patients with dual pathology showed a tendency for earlier epilepsy onset and longer epilepsy duration compared with patients presenting with plain focal cortical dysplasia (Bast et al., 2006).

The presence of cortical dysplasia in patients who underwent temporal lobectomy was first described by Taylor et al. (1971). Since then, an association of hippocampal sclerosis with macroscopic or microscopic cortical dysplasia in the temporal lobe has been reported as a quite common pathology with dysplastic features found in the temporal neocortex in 10-50% of patients with hippocampal sclerosis (Fauser et al. 2006).

Patients with hippocampal sclerosis and associated cortical dysplasia are difficult to distinguish from the patients with isolated hippocampal sclerosis on the basis of general clinical features, MRI findings, or ictal clinical semiology. The
clinical significance of temporal pole MRI abnormalities in temporal lobe epilepsy patients with hippocampal sclerosis is still unclear (Marusic et al., 2007).

Mild ipsilateral anterior temporal changes can be seen on MRI of a substantial number of patients with hippocampal sclerosis and represent by some authors an abnormal persistent immature appearance, including an abnormality of myelin or myelination (Mitchell et al. 2003).

MRI volumetric and PET studies have found group differences between patients with isolated hippocampal sclerosis and hippocampal sclerosis associated with cortical dysplasia. The presence of bilateral temporal lobe atrophy is suggestive of a more widespread (bilateral) temporal lobe involvement in patients with hippocampal sclerosis and cortical dysplasia and in patients with isolated hippocampal sclerosis, the most prominent hypometabolism was in the anterior and mesial temporal lobe, whereas in dual pathology, it was in the lateral temporal lobe. However, these group differences may not distinguish associated cortical dysplasia preoperatively in individual patient (Diehl et al. 2004).

In presurgical evaluation, the presence of dual pathology must be taken into consideration because of the common association between focal cortical dysplasia and hippocampal
sclerosis. There were patients that on the ground of MRI investigation were thought to have focal cortical dysplasia and postoperatively after histopathological evaluation presented hippocampal sclerosis. Others that were diagnosed with plain hippocampal sclerosis per MRI showed a dual pathology in the histopathological examination performed postoperatively (Tassi et al., 2002).

Reports on the postoperative outcome of patients with dual pathology are controversial. Early studies reported that patients with hippocampal sclerosis and associated microscopic cortical dysplasia have a higher risk for seizure recurrences after epilepsy surgery as compared with patients with only hippocampal sclerosis. More recent investigations, however, demonstrates that these patients can have a very favorable outcome provided that both pathologies were removed. Therefore, the distinction between this group of patients and those with isolated hippocampal sclerosis is important and may assist in the presurgical diagnosis and improve the postoperative seizure outcome (Marusic et al., 2007).

In epilepsy caused by focal cortical dysplasia, surgical resection is an important treatment modality. The postoperative rate of focal cortical dysplasia patients rendered seizure-free varies from about 50% to approximately 65% in major patient collectives (Bast et al., 2006).
Various histopathological subtypes were shown to have a diverse postoperative prognosis: the proportion of patients rendered seizure-free as a result of surgical treatment was significantly lower in focal cortical dysplasia type 2 (especially type 2a) compared with milder forms of focal cortical dysplasia (mild cortical dysplasia/ focal cortical dysplasia type 1) (Fauser et al., 2004).

The frequently encountered resistance to treatment is mainly attributed to the following two factors:

- **Intrinsic epileptogenicity:** It is presumed, that the affected tissue in focal cortical dysplasia is itself highly epileptogenic, which is a distinct characteristic when compared with non-dysplastic lesions.

- **Multi-drug-transporter:** An activation of diverse multi-drug-transporter proteins in glial cells and dysplastic neurones can be shown in the case of focal cortical dysplasia. MDR1 was proven to be elevated in focal cortical dysplasia tissue in a number of studies. Furthermore, multidrug-resistance associated protein 1 (MRP 1) and the major vault protein may act as upregulated drug-transporters in focal cortical dysplasia. (Bast et al., 2006)
Periventricular nodular heterotopias

Heterotopias are malformations of cortical development characterized by the presence of apparently normal brain cells in abnormal positions. Three broad categories are recognized: band heterotopia (*double cortex*), individual misplaced neurons in the white matter (*neuronal heterotopia*) and nodules of grey matter within the white matter (*nodular heterotopia*) (*Tassi et al., 2005*). *Barkovich and Kuzniecky, (2000)* did not include neuronal heterotopia among malformations of cortical development due to abnormal migration; however, in the recent classification (*Barkovich et al., 2001*), conditions of abundant neurons in the white matter are again considered as being due to abnormal neuronal migration.

Nodular heterotopia are further divided into: subependymal heterotopia (subsuming periventricular nodular heterotopia), which appears on MRI as nodular subependymal masses having the same signal intensity as cortical grey matter; and subcortical heterotopia, which appear as irregular clusters of nodules of grey matter within the white matter (*Barkovich et al., 2001*).

Periventricular nodular heterotopias are among the most common malformations of cortical development and affected patients are frequently characterized by focal drug-resistant
epilepsy. Periventricular nodular heterotopias are made up of round nodular masses of normal neurons and glial cells with no laminar organization, located close to the periventricular germinal matrix, and hence called periventricular or subependymal nodular heterotopias. For this particular location within the brain and the normal features of the heterotopic cells, it has been considered the result of a primary failure of neuronal migration \textit{(Battaglia et al., 2006)}.

Periventricular nodular heterotopias may present as malformations attributable to a generalised abnormal cortical development or in focal or multifocal abnormalities. Generalised periventricular nodular heterotopias consist of bilateral contiguous nodules creating an irregular bumpy surface lining the ventricular wall. Focal or multifocal periventricular nodular heterotopias are considered a localised abnormality with multiple but not contiguous nodules. Both generalised and localized nodular heterotopia are attributable to abnormal neuronal migration and may be isolated or associated with other cortical and brain malformations \textit{(D’Orsi et al., 2004)}.  

Bilateral and symmetrical periventricular nodular heterotopias occur mostly in female subjects; it may be familial and causally related to point mutations of the \textit{FLNI} gene. In
In addition to these cases, familial patients with bilateral periventricular nodular heterotopia not related to FLN1 mutations, and sporadic female patients with bilateral but clearly asymmetrical periventricular nodular heterotopias have been reported. Unilateral periventricular nodular heterotopias are frequently located in the posterior paratrigonal region of the lateral ventricles and may extend into the white matter to involve adjacent neocortical and archicortical areas (Battaglia et al., 2006).

Large periventricular nodular heterotopias extending from the subependymal region to involve overlying malformed cortical areas in different lobes have been termed subcortical heterotopias, but it is not yet clear whether periventricular and subcortical heterotopia are separate entities or different extensions of the same brain dysgenesis (Barkovich, 2000).

Periventricular nodular heterotopias probably result from an arrest in the migrational progress of neuroblasts from the periventricular layer to the cortex, which usually occurs maximally between the 7th and 16th gestational weeks, along radial glial fibres or is due to a failure of programmed cell death of groups of neuroblasts within the periventricular germinal matrix (Aghakhani et al., 2005).
When there is a primary, limited, and pure deficit in neuronal migration onset, the remaining neuroblasts may migrate normally to form the regular six layered cortex and periventricular nodular heterotopias only appear. When the ongoing process of migration or of the later stage of neuronal migration and cortical organisation are also impaired, subcortical heterotopia or polymicrogyria and schizencephaly may develop with periventricular nodular heterotopias (D’Orsi et al., 2004).

Subependymal or periventricular heterotopia is the most commonly identified type of heterotopia in clinical practice. The prevalence of periventricular nodular heterotopias in patients with epilepsy is unknown. The associated epilepsy syndrome is variable and seizures may be generalized or focal, often suggesting mesial or neocortical temporal and parieto-occipital onset. Periventricular nodular heterotopias may either be the epileptogenic source or part of a more widespread epileptogenic network involving the hippocampus, and the overlying or distant neocortex (Aghakhani et al., 2005).

Periventricular nodular heterotopias are considered to be associated with developmental delay and epilepsy, but a wide variety and heterogeneity of clinical pictures are often present. Epilepsy can begin in the second or third decade of life or
earlier, with seizures ranging from rare to very frequent, often resistant to polytherapy. Most patients present with partial seizures, exceptionally with status epilepticus. Mental retardation, usually absent or mild, can also be severe and associated with neurological deficits and dysmorphic features (D’Orsi et al., 2004).

Tuberous sclerosis complex

Tuberous sclerosis or tuberous sclerosis complex is a multisystemic disorder involving primarily the central nervous system, the skin, and the kidney. A prevalence of 1:30 000 – 50 000 has been reported. In the brain, the characteristic features are cortical tubers, subependymal nodules and giant cell tumors. Cortical tubers are more directly related to epileptogenesis. They are identified by their nodular appearance, firm texture, and variability in site, number and size. Microscopically, the tubers consist of subpial glial proliferation with orientation of the glial processes perpendicular to the pial surface, and an irregular neuronal lamination with giant multinucleated cells that are not clearly neuronal or astrocytic. The junction between gray and white matter is indistinct and may be partly demyelinated. These pathological changes are similar to those seen in focal cortical dysplasia. Cortical tubers are usually well visualized by MRI as enlarged gyri with atypical shape and
abnormal signal intensity, mainly involving the subcortical white matter (Guerrini et al., 2003).

Tuberous sclerosis complex is transmitted as an autosomal dominant trait, with variable expression seen within families. Recurrence in siblings of non-affected parents has rarely been reported. Between 50 to 75% of all cases are sporadic. Linkage studies have allowed the identification of two loci for tuberous sclerosis complex (TSC), mapping to chromosome 9q34 (TSC1) and 16p13.3 (TSC2) (Povey et al., 1994). About 50% of the familial cases are linked to TSC1 (Van Bakel et al., 1997).

Clinical assessment indicated that sporadic patients with TSC1 mutations had, on average, a milder disease than did patients with TSC2 mutations, including a lower frequency of seizures, moderate to severe mental retardation, fewer subependymal nodules and cortical tubers, less severe kidney involvement, no retinal hamartomas, and less severe facial angiofibroma (Dabora et al., 2001).

Epileptic seizures are frequent in tuberous sclerosis complex. They usually begin before the age of 15, mostly in the first 2 years of life: 63.4% before one year, 70% before two years. Infantile spasms are the most common manifestation of epilepsy in the first year of life, sometimes preceded by partial seizures (Guerrini et al., 2003).
Glioneuronal tumors

Long-term epilepsy associated glioneuronal tumours mainly comprise gangliogliomas and dysembryoplastic neuroepithelial tumours (Blumcke et al., 2009). Both neoplasms are rare, with an incidence of approximately 1.3% of all brain tumours (Blumcke and Wiestler, 2002). Any lobe can be affected, but temporal lobe locations appear to be far more frequent for both gangliogliomas and dysembryoplastic neuroepithelial tumors (Guerrini et al., 2003).

They are frequent in children and young adults suffering from pharmacologically intractable focal epilepsy. However, the differentiation between a neoplastic and dysplastic lesion is often difficult to obtain, either using electrophysiology (EEG recording), imaging, histopathology or molecular-genetic analysis (Blumcke et al., 2009).

In large series of patients with surgically-treated drug-resistant epilepsy due to neoplastic lesions, gangliogliomas and dysembryoplastic neuroepithelial tumor represent the majority (50 – 75%) of histopathologically diagnosed lesions (Zentner et al., 1997).

Gangliogliomas are histologically characterised by a glioma component intermixed with an atypical neuronal or ganglion cell component. Atypical neuronal or ganglion cells
are frequently binucleate. Cell proliferation studies show that the tumour growth rate is slow. Dysembryoplastic neuroepithelial tumors are similar to gangliogliomas, but cytological atypia are more rare. Dysplastic neurons frequently lie adjacent to the neoplastic lesions (Prayson, 2001).

Neuroradiological studies typically show a hypodense lesion on CT scan, with possible associated hyperdense calcified lesions. Overlying skull can be deformed in superficially located lesions. MRI scans show a hyperintense T1 lesion that is usually peripherally enhanced after gadolinium administration. Gray and white matters are both involved. A well demarcated, multilocular appearance is typically seen (Guerrini et al., 2003).

Dysplastic disorganization of the cortex near but separate from the tumour has often been observed and particularly studied in dysembryoplastic neuroepithelial tumors (Prayson et al., 1993). The large majority of glioneuronal tumours present either with mild malformations of cortical development or with focal cortical dysplasia type IA; only a few cases have been reported to be associated with focal cortical dysplasia type II (Ferrier et al., 2006).

Whether focal cortical dysplasia occurring in association with a glioneuronal tumour represents a distinct entity (different from isolated focal cortical dysplasias) is a matter of ongoing
debate. The maldevelopmental and dysembryoplastic nature of glioneuronal tumours is likely to compromise always normal maturation of the adjacent neocortex. However, none of the current classification systems for tumours of the central nervous system, nor malformations of cortical development specifically address or clarify this issue (Blumcke et al., 2009).

Clinical presentation is with drug resistant partial epilepsy. In a population of 89 patients with dysembryoplastic neuroepithelial tumors, partial seizures were the first clinical signs in 75%, while only 9% had neurological deficits consisting of quadranopsia. Epilepsy started at a mean age of nine years (range 1-20 years) and proved resistant to different antiepileptic medications. Complete surgical removal of the lesion was associated with remission of epilepsy in all patients (Guerrini et al., 2003).

The cellular mechanisms underlying epileptogenicity of glioneuronal tumours and/or the perilesional cortical tissue are still not clearly defined. Intrinsic epileptogenicity is supported by electrocorticography, surgical and immunocytochemical studies, suggesting the presence of a hyperexcitable neuronal component (Aronica et al. 2001a).

Developmental alterations compromising the balance between excitation and inhibition are likely to play a role in the pathogenesis of epileptic focal discharges in patients with
glioneuronal tumours (Aronica et al., 2007a). Recent evidence points to the inflammatory response as a contributing factor in the epileptogenicity of these developmental lesions (Ravizza et al., 2006). Similarly to other brain tumours (such as gliomas), the peritumoral region may also be relevant for the generation and propagation of seizure activity (Van Breemen et al., 2007).

Long-term follow-up studies of a large series of patients revealed favorable outcomes for patients with supratentorial glioneuronal tumours, with only rare cases of tumour recurrence or malignant progression to glioblastoma reported for gangliogliomas (Luyken et al., 2003). Limited information is available about recurrence or malignant transformation of dysembryoplastic neuroepithelial tumors (Maher et al., 2008).

The large majority of patients with glioneuronal tumours became seizure free after surgical resection. Short duration of epilepsy before surgery, absence of secondary generalized seizures or status epilepticus, absence of additional pathologies and complete resection predicted a better post-operative seizure outcome (Luyken et al., 2003).

Thus, an early identification of glioneuronal tumours associated with chronic intractable epilepsy, followed by a prompt referral to epilepsy surgery centers provides the best chance for curing epilepsy and preventing its recurrence and
possible malignant transformation. However, it has not been systematically studied whether failure of post-surgical seizure relief results from unrecognized cortical disorganization in the vicinity of the resection site (Blumcke et al., 2009).

Do seizures start within the lesion or the perilesional region?

Based on the focal, circumscribed nature of the lesions in most of these malformations of cortical development, it would seem to make intrinsic sense that seizures originate within the lesions. The high success rate of “lesionectomy” during epilepsy surgery, with many studies reporting over a 60–75% seizure-free rate, also supports the idea that the lesions directly produce seizures (Aronica et al., 2001a).

However, this still leaves a substantial minority of patients that continue to have seizures following lesionectomy, suggesting that the epileptogenic zone was not contained within the lesion in those cases. Furthermore, the success of lesionectomy in eliminating seizures may have other interpretations: The margins of resection typically contain some “normal” perilesional tissue, which may actually be the primary source of the seizures. Alternatively, perilesional cortex, immediately adjacent to or even distant from the lesion, may generate the seizures, but may be somehow dependent on the
lesion for epileptogenesis; removal of the lesion eliminates this driving force for seizure generation within the remaining cortex (*Wong, 2008*).

Finally, studies correlating radiographic and pathological data increasingly indicate that areas of “normal”-appearing cortex on MRI in patients with other discrete regions of malformations of cortical development often contain subtle histopathological abnormalities (*Porter et al., 2003*).

- **In tuberous sclerosis complex**

  In tuberous sclerosis complex, a variety of clinical studies, including electrophysiological and radiographic investigations, suggest that cortical tubers are the primary site of epileptogenesis. EEG often identifies both interictal epileptiform abnormalities and seizures originating from the immediate region of a putative epileptogenic tuber on MRI. Furthermore, nuclear medicine radiographic studies, such as PET and SPECT, often point to specific tubers as being the source of seizures (*Koh et al., 2000*).

  Finally, surgical approaches for epilepsy specifically targeting tubers often result in seizure freedom in at least 75% of patients strongly supporting the idea that tubers are the source of the seizures in these cases (*Weiner et al., 2006*).
Despite the abundant clinical evidence implicating tubers as the epileptogenic foci in tuberous sclerosis complex, a number of limitations reduce the certainty of this conclusion. In many cases, radiographic and electroencephalographic data do not have a high enough spatial resolution to clearly distinguish an epileptogenic source from within a tuber itself versus the adjacent perituberal region. In addition, most surgical resections also include at least some margin of normal-appearing cortex surrounding the tuber, making it difficult to rule out the perituberal region as the source of seizures and the reason for success with surgery. Furthermore, some patients continue to have seizures despite an appropriately targeted tuberectomy. Finally, most of the clinical data supporting the importance of tubers derive from series of tuberous sclerosis complex patients that underwent epilepsy surgery, which likely represents a biased, preselected group. Other tuberous sclerosis complex patients, who were not deemed to be good surgical candidates, as well as patients who failed epilepsy surgery, may have other mechanisms of epileptogenesis that are not as tightly linked to tubers (Wong, 2008).

Some clinical evidence suggests that the nontuber regions of cortex could also be a source of epileptogenesis. Quantitative MRI studies indicate that tuberous sclerosis complex patients
have diffusely decreased cortical grey matter volume, not specifically related to cortical tubers \textit{(Ridler et al., 2001)}. 

Also, diffuse cellular abnormalities have been reported in some cases of tuberous sclerosis complex brains independent of tubers, such as atypical poorly differentiated cells and decreased neuronal counts \textit{(Roske et al., 2003)}. 

Although the relevance of these more diffuse radiographic and histological abnormalities to epilepsy is not established, they at least raise the possibility that nontuber cortex is abnormal and may be capable of generating seizures \textit{(Wong, 2008)}. 

In addition, more direct clinical evidence for the role of nontuber cortex in causing seizures is seen in rare reports of tuberous sclerosis complex patients with intractable epilepsy, who become seizure free following surgical resection of normal-appearing, tuber-free brain tissue \textit{(Wang et al., 2007)}. 

\begin{itemize}
  \item \textbf{In focal cortical dysplasia}
    
    Clinical evaluations, including EEG, MEG, and various imaging methods, frequently provide evidence that seizures originate intrinsically from within the focal cortical dysplasia evident on MRI \textit{(Bast et al., 2004)}. 
\end{itemize}
Surgical resection of focal cortical dysplasia results in seizure freedom in at least 50% of patients, again supporting the concept of the epileptogenic foci being contained within the focal cortical dysplasia (Tassi et al., 2002).

There is substantial clinicopathological evidence that seizures can also arise from regions beyond the focal cortical dysplasia, or at least outside the area of the focal cortical dysplasia that is grossly evident on MRI. A likely explanation for surgical failures in patients with focal cortical dysplasia is that the true area of focal cortical dysplasia may extend on the microscopic level beyond the region of obvious abnormality apparent on MRI (Gomez-Anson et al., 2000).

Limited by the resolution of imaging technology as the resolution of imaging methods continues to improve, brain regions that appear “normal” by current techniques may eventually be identified as “lesional.” In fact, a retrospective diagnosis of focal cortical dysplasia is often made by pathological analysis of brain tissue resected from patients with intractable epilepsy, who had no evidence of focal cortical dysplasia on preoperative MRI (Bautista et al., 2003).

Consistent with this idea, advanced quantitative MRI techniques have found abnormalities in grey matter volume
beyond the regions of focal cortical dysplasia identified by conventional visual inspection \((Wong, 2008)\).

- **In gangliogliomas**

  Perilesional mechanisms of epileptogenesis are also strongly implicated in cases of ganglioglioma. Epileptiform discharge patterns emanating from ganglioglioma on electrocorticography (Ferrier et al., 2006) and the success of lesionectomy in eliminating seizures (Aronica et al., 2001a), suggest the possibility that seizures could directly start within the ganglioglioma itself.

  However, the limited spatial resolution of this type of clinical data, as similarly discussed above for tuberous sclerosis complex, makes it difficult to rule out that peritumoral mechanisms actually account for these clinical observations. There are limited electrophysiological data documenting whether cells in ganglioglioma are electrically excitable. Thus, many studies have focused on secondary effects of the tumor on peritumoral regions as the basis for epileptogenesis in ganglioglioma \((Wong, 2008)\).

  In fact, electrophysiological data from both human tissue and animal models indicate that the regions adjacent to or at the border of gliomas have the highest potential to generate epileptiform activity \((Patt et al., 2000)\).
Is epileptogenesis primarily a result of circuit abnormalities or cellular/molecular defects?

Epileptogenesis in malformations of cortical development is primarily due to circuit abnormalities or cellular and molecular defects. Seizures clearly consist of synchronous electrical activity reverberating through complex neuronal networks and thus ultimately must always include abnormalities on the circuit level. However, from a pathophysiological standpoint, mechanisms of epileptogenesis could involve either primary changes in circuit organization or initial cellular and molecular defects that secondarily translate to the network level. On the extremes, circuit abnormalities (the epileptic circuit) might consist of aberrant connectivity of neurons that are otherwise completely normal in function, whereas cellular/molecular mechanisms (the epileptic neuron) would involve a defect involving intrinsic neuronal function in the context of normally wired and fully operational circuits. Ultimately, both network and cellular/molecular abnormalities will stimulate epileptogenesis by upsetting the normal physiological balance between excitation and inhibition in the brain (Wong, 2008).

- **In tuberous sclerosis complex**
  
  *Valencia et al. (2006)* reported some limited immunohistochemical evidence for anomalous GABAergic
inhibitory circuits within cortical tubers. With intracellular recordings of normal-appearing neurons in nontuber tissue resected from a tuberous sclerosis complex patient, there was evidence of neuronal hyperexcitability but no impairment of synaptic inhibition (Wang et al., 2007).

On the cellular level, a popular hypothesis about seizure generation in tuberous sclerosis complex is that an abnormal cell type, in particular the giant cell in tubers, could serve as an intrinsic “pacemaker” that initiates and drives epileptiform activity and seizures. Contrary to the “pacemaker” hypothesis, giant cells from tuberous sclerosis complex patients were actually found to be electrically inexcitable, with no evidence of voltage-activated sodium or calcium currents. Cytomegalic neurons from tuberous sclerosis complex specimens were capable of generating action potentials, including repetitive calcium spikes in response to stimulation, and thus have potential for contributing to epileptic discharges, but showed no evidence of intrinsic pacemaker properties. Thus, the available physiological data do not support the concept that giant cells or other dysmorphic neurons within tubers are, by themselves, the primary generators of epileptiform activity in tuberous sclerosis complex (Wong, 2008).

The most evidence for potential abnormalities promoting epileptogenesis in tuberous sclerosis complex arguably exists
on the molecular level, largely derived from single-cell polymerase chain reaction (PCR) and microarray analysis of cells from tubers resected from tuberous sclerosis complex patients with intractable epilepsy. Molecular characterization revealed increased mRNA expression of specific glutamate NMDA receptor subunits and a decrease in specific GABA_A receptor subunits in giant cells and dysplastic neurons. These specific changes in neurotransmitter expression within tubers could have obvious effects in promoting hyperexcitability and seizures (White et al., 2001).

- **In focal cortical dysplasia**

  On the circuit level, both immunohistochemical and electrophysiological studies indicate that abnormal, potentially hyperexcitable networks exist within focal cortical dysplasia tissue specimens resected from patients with intractable epilepsy (Wong, 2008).

  A decrease or abnormal organization of GABAergic interneurons within focal cortical dysplasia was demonstrated as assayed immunocytochemically by markers - parvalbumin, calbindin, or glutamic acid decarboxlyase. Also, Intracellular recordings from pyramidal neurons in neocortical slices from human dysplastic cortex demonstrated physiological evidence
of decreased GABA-mediated synaptic inhibition (Calcagnotto et al., 2005).

While there is strong evidence for impaired GABAergic circuits in focal cortical dysplasia, which could clearly promote hyperexcitability and seizures, less is known about the organization of circuits within and around focal cortical dysplasia that actually generate the seizures. Balloon cells do not appear to receive synaptic contacts (Alonso-Nanclares et al., 2005).

Small subpopulation of cytomegalic interneurons has been described in focal cortical dysplasia that exhibit intrinsic bursting behavior (Andre et al., 2007). Furthermore, basket-like clusters of GABAergic interneurons often surround cytomegalic neurons and could serve to synchronize epileptiform activity (Alonso-Nanclares et al., 2005).

It is conceivable that a primary impairment of GABAergic circuits could lead to disinhibition, synchronization, and hyperexcitability of otherwise normal-appearing cortical pyramidal neurons within and surrounding the regions of focal cortical dysplasia (Calcagnotto et al., 2005).
Dysplastic and heterotopic pyramidal neurons microdissected from human focal cortical dysplasia specimens exhibit decreased expression of specific GABA_A receptor subunits (Crino et al., 2001).

Immunocytochemical and single-cell mRNA amplification techniques have shown that specific subunits of NMDA, AMPA, and metabotropic glutamate receptors are altered, typically increased, in dysplastic neurons from focal cortical dysplasia (Aronica et al., 2003a). Physiologically, NMDA receptors of pyramidal neurons from focal cortical dysplasia display decreased sensitivity to magnesium inhibition, which could promote increased neuronal excitability (Andre et al., 2004).

While glutamate and GABA receptors tend to receive the most attention in mechanisms of epileptogenesis, a number of other molecular players can also influence excitability in focal cortical dysplasia. Some evidence indicates that epileptic tissue from focal cortical dysplasia may recapitulate or maintain immature properties. The immature brain tends to have a decreased seizure threshold which may, in part, be due to a paradoxical excitation due to GABA during early brain development. While GABA causes hyperpolarization and inhibition of neurons in adulthood, a relatively elevated intracellular chloride concentration in immature neurons leads
to depolarization and excitation by GABA in neonatal rodent and human cortex (*Wong, 2008*).

Astrocytes control the extracellular levels of excitatory ions and neurotransmitters, such as potassium and glutamate, which may directly affect neuronal excitability. In addition, astrocytes recently have been shown to release glutamate and other substances as intrinsic “gliotransmitters,” which can directly stimulate neurons and participate in synaptic signaling in the so-called tripartite synapse (*Haydon, 2003*).

Given the prominent role of mature glial cells and glioneuronal progenitors cells in the malformations of cortical development with abnormal glioneuronal proliferation, it would be logical to hypothesize that glial abnormalities might also contribute to epileptogenesis in these malformations of cortical development, such as tuberous sclerosis complex and focal cortical dysplasia. Histological abnormalities in glia in tubers, such as the presence of poorly differentiated giant cells with mixed glial-neuronal properties and astrocyte proliferation, suggest a possible role of glia in epileptogenesis in tuberous sclerosis complex. There are fewer data related to astrocytic regulation of glutamate and potassium in focal cortical dysplasia, although the similarities in histological features of glia in these malformations of cortical development compared with tuberous sclerosis complex make it likely that analogous
astrocytic abnormalities occur in all these disorders (Wong, 2008).

- **In gangliogliomas**

  Less is known about the effects of ganglioglioma on circuit properties and network excitability, although, as discussed earlier, it may be neuronal networks at the border or perilesional regions of ganglioglioma that are the most epileptogenic (Patt et al., 2000). Evidence has been found for decreased GABAergic interneurons in perilesional epileptic networks adjacent to ganglioglioma (Aronica et al., 2007b).

  On the cellular and molecular level, a number of abnormalities in glutamate and GABA receptors have been documented in ganglioglioma, which are analogous to tuberous sclerosis complex or focal cortical dysplasia, again suggesting that these malformations of cortical development share common pathophysiological origins and mechanisms of epileptogenesis (Wong, 2008).

  Immunocytochemical studies indicate that neuronal components of ganglioglioma highly express NMDA and AMPA receptors (Aronica et al., 2001b). Single-cell mRNA analysis detected changes primarily in metabotropic glutamate receptors in ganglioglioma, but also demonstrated reduced expression in GABA\(_A\) receptor subunits (Samadani et al., 2007).
Expression of drug transporters in pathological lesions associated with refractory epilepsy

*Tishler et al. (1995)* measured *MDR1* expression in 19 patients undergoing respective epilepsy surgery, 15 of whom received temporal lobectomy for a mixture of pathologies (mostly hippocampal sclerosis). *MDR1* mRNA level was found to be >10 times higher in 11 of the 19 resected samples compared with controls (“normal” brain tissues resected during removal of arteriovenous malformations).

*Sisodiya et al. (2002)* stained both P-gp and MRP1 in astrocytic cells, but not capillary endothelium, in the hippocampus in cases of hippocampal sclerosis.

More recently, *Aronica et al. (2004)* performed detailed immunostaining studies in brain sections from 16 patients with hippocampal sclerosis and found upregulation of P-gp and MRP2 in capillary endothelium.

The other group of pathologic lesions frequently associated with intractable epilepsy that has been more widely investigated for over-expression of efflux transporters is malformations of cortical development. focal cortical dysplasia tissues removed from patients with refractory epilepsy showed intralesional (but not perilesional) induction of MRP1 in
dysplastic neurons, balloon cells, and glial processes around blood vessels, whereas P-gp over-expression was observed primarily in the glial component and capillary endothelium (Sisodiya et al., 2001).

In patients with uncontrolled seizures associated with tuberous sclerosis complex, immunostaining in resected cortical tubers for P-gp and MRP1 was observed in dysplastic neurons, balloon cells, astrocytes, and microglial cells, whereas only P-gp was upregulated in blood vessels (Lazarowski et al., 2004).

In addition to hippocampal sclerosis and malformations of cortical development, over-expression of P-gp or MRP or both has been noted in other epileptic pathologies. Positive immunostaining of both transporters was observed in reactive astrocytes within dysembryoplastic neuroepithelial tumors (Sisodiya et al., 2002).

In ganglioglioma, removed from patients with intractable epilepsy, both P-gp and MRP1 were detected in neuronal cells, MRP in glial cells, and P-gp in capillary endothelium within the lesion (Aronica et al., 2003b).
MANAGEMENT

- Anti-epileptic drugs
- Epilepsy surgery
- Ketogenic diet
- Vagus nerve stimulation
- Treatments under investigation
Although relative drug-resistant epilepsy can be diagnosed after failure of two anti-epileptic drugs, absolute drug resistance requires failure of six anti-epileptic drugs, as a significant minority of patients (16.6%) is rendered seizure free by addition of newly administered anti-epileptic drugs even after failure of two to five antiepileptic drugs (Schmidt, 2009).

The chances of controlling epilepsy decline sharply after failure of the second or third antiepileptic drug trial. In fact, some clinicians would argue against trying another antiepileptic drug in these patients, who may be candidates for surgical procedures that have high rates of success (Berg, 2004).

Common causes of treatment failure, such as poor compliance or inappropriate selection of first-line antiepileptic drugs, should be addressed early on by the treating physician. Nonadherence to the prescribed regimen is a very common cause of uncontrolled seizures, so it is critical to maintain a good rapport with the patient and to inquire about reasons for noncompliance (Pati and Alexopoulos, 2010).

Importantly, the prognosis for most patients with newly diagnosed epilepsy, whether good or bad, becomes apparent within a few years of starting treatment. A history of a lack of a sustained seizure-free period for 12 consecutive months, in spite of two or three suitable and tolerated antiepileptic drugs, is a definite red flag for clinicians and should prompt referral to a specialist center (Kwan and Brodie, 2000).
Evaluating patients with suspected pharmacoresistant epilepsy demands a systematic and holistic approach with equal emphasis on quality of life and psychosocial and cognitive factors (Siegel, 2004).

The medical, social, and economic consequences of poorly controlled seizures can be enormous. Recurrent seizures are associated with significant risks for death, physical injury, cognitive impairment, and psychosocial problems. Frequent seizures not only influence quality of life, morbidity, and mortality in epilepsy, but also significantly increase costs (Schmidt, 2009).

The clinical assessment should be based on the following principles:

1. **Review and confirm** the diagnosis of epilepsy with the help of a careful history, video-EEG, and imaging. When seizures cannot be controlled with drugs, it is important to verify that the events in question are indeed epileptic. Continuous video-EEG monitoring may be necessary to capture and characterize the clinical manifestations and corresponding EEG changes.

2. **Identify the cause**, type of seizure or seizures, and syndromic classification, if any.

3. **Review past and present medications**, doses, efficacy, and side effects. Consider the possibility of drug interactions.

4. **Choose antiepileptic drugs** primarily on the basis of the type of seizures and the individual clinical scenario: Which
drug is likely to be most efficacious with the fewest side effects, and which one is appropriate for the patient’s comorbidities and concomitant medications?

5. **Discuss issues** such as seizure precautions, lifestyle modifications, psychosocial dysfunction, and sudden unexpected death. *(Pati and Alexopoulos, 2010)*

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**Fig. (4) Clinical approach to patients with pharmacoresistant epilepsy** *(Pati and Alexopoulos, 2010).*
Anti-epileptic drugs

In chronic epilepsy (more than 5 years), the addition of a new anti-epileptic drug provided a seizure freedom of 17% and a 50–99% seizure reduction of 25%. For those who did not respond to the first trial, a similar benefit might be expected for at least 2 more trials. At the end, 28% of the patients were seizure free. The application of a systematic protocol to the treatment of refractory epilepsy using a new anti-epileptic drug might improve seizure control in a substantial proportion of cases. The nihilistic view that intractability is inevitable if seizure control is not obtained within a few years of the onset of therapy is incorrect (Luciano and Shorvon, 2007).

In refractory epilepsy, it is convenient to perform a systematized management of anti-epileptic drug: (1) increase until the maximum tolerable dose; (2) if no response, replace the anti-epileptic drug, if there is a partial response, add another anti-epileptic drug which should be chosen based on the mechanism of action of the first anti-epileptic drug (e.g. lamotrigine and valproate are synergic), its efficacy and adverse effects (Brodie, 2005).

Epilepsy surgery

Resective surgery is based on removal of the entire epileptogenic area without causing a permanent neurological
deficit. The localization of the epileptogenic zone in focal epilepsy is typically based on seizure semiology, interictal and ictal EEG findings, as well as FDG-PET, SPECT and MRI lesions (Rosenow and Luders, 2001).

Is the patient a candidate for epilepsy surgery?

The rationale for surgical management of pharmacoresistant focal epilepsies is to eliminate or significantly reduce the patient’s propensity for spontaneous seizures by removing the epileptogenic focus (Pati and Alexopoulos, 2010).

Several factors need to be considered in the course of a comprehensive and multidisciplinary specialized evaluation before answering the critical question of whether a patient with intractable seizures may be a candidate for respective epilepsy surgery.

1. Is the epilepsy diagnosis correct?
2. Is the epilepsy focal? Have the following possibilities been excluded: generalized or multifocal epilepsy, situational or provoked seizures, or an epilepsy syndrome with spontaneous remission?
3. Do seizures remain poorly controlled despite adequate pharmacologic trials?
4. If so, do the seizures or medication side effects significantly affect the patient’s quality of life?
5. Can an epileptogenic lesion be seen on MRI, and what is the suspected etiology?
6. Is there converging evidence for a single epileptogenic focus?
7. Are there abnormalities elsewhere in the brain?
8. What are the chances of a good outcome in terms of seizure control and improvement in quality of life?
9. What are the risks of surgery, and how do these compare with the risks of not having surgery?
10. What are the patient’s perceptions and attitudes toward epilepsy surgery? (Alexopoulos and Najm, 2009)

Focal epilepsy with a lesion not adjacent to the eloquent cortex and concordant with semiology, ictal EEG, interictal EEG and PET/SPECT may be removed based solely on surface evaluation. In the case of focal epilepsy without a lesion, a lesion adjacent to an eloquent cortex or if there is no concordance between the different zones, invasive monitoring is recommended (Rosenow and Luders, 2001).
Fig. (5) Specialized diagnostic and treatment options for patients with pharmacoresistant epilepsy (Pati and Alexopoulos, 2010).

Preoperative counseling is essential for the patient and his or her family, addressing the goals, risks, and benefits of the surgery. Treatment decisions should take into account the possible impact of surgery on the patient’s medical and psychosocial circumstances (risks of ongoing seizures vs
surgical intervention; impact on the patient’s independence, employment status, emotional well-being, and psychiatric and other comorbidities) *(Pati and Alexopoulos, 2010)*.

**Curative procedures**

Curative procedures include lobectomy, lesionectomy, and multilobar or hemispheric surgery (hemispherectomy).

**A. Anterior temporal lobectomy and hippocampectomy**

More than half of the procedures in surgical epilepsy programs are anterior temporal lobe resections. Mesial temporal lobe epilepsy associated with hippocampal sclerosis is the most common form of focal epilepsy, with around 60% of the patients having temporal resection. 60–70% of the patients are free of seizures at 1–2 years of follow up and only 58% are seizure free at 10 years *(Duncan, 2007)*.

**B. Lesionectomy and lobectomy**

Lesionectomy and lobectomy are respective approaches targeting seizure foci outside the temporal lobe (most often in the frontal lobe, less commonly in the parietal or occipital lobes) or within the temporal lobe but outside the hippocampus (neocortical temporal lobe epilepsies). Patients with seizures due to structural lesions that are visible on MRI (“lesional epilepsies,” eg, cavernous angiomas or circumscribed low grade
tumors) may become seizure-free after limited resections targeting the lesion itself (lesionectomy) or extending to involve part of a lobe or an entire lobe (lobectomy) (*Pati and Alexopoulos, 2010*).

Extratemporal lobe surgery for focal epilepsy accounts for less than half of all epilepsy operations. In frontal lobe epilepsy surgery, the probability of becoming seizure free is 55.7% at 1 year, 45.1% at 3 years, and 30.1% at 5 years. The subset of patients with favorable prognostic factors – an MRI lesion restricted to one frontal lobe, complete resection, and a regional or lateralized ictal scalp EEG pattern – show a seizure free outcome approaching that seen after temporal lobectomy, with 50–60% being seizure free at 3 years. Regarding etiology, patients with low-grade tumors have the best outcome (62%), followed by patients with MRI malformations of cortical development (52%) (*Beleza, 2009*).

On the other hand, identifying the epileptogenic focus in patients with no visible structural abnormality on MRI (“nonlesional epilepsies”) can be challenging and usually requires intracranial investigations. In this instance, the aim of surgery is to resect regions that are electrographically abnormal. In general, the postoperative outcome is less favorable in nonlesional focal epilepsies than in lesional epilepsies (*Cascino, 2004*).
C. Multilobar resections and hemispherectomy

Multilobar resections and hemispherectomy are indicated when seizures arise from extensive, diffuse, or multiple regions of a single hemisphere (Pati and Alexopoulos, 2010).

If the neurologic function supported by the abnormal hemisphere is intact, a tailored multilobar resection aims at eliminating the epileptogenic focus without creating new deficits. If, however, the underlying hemispheric abnormality is associated with significant contralateral hemiparesis, hemiplegia, or visual field deficits, the need to preserve function does not limit surgery, and hemispherectomy can be considered. Hemispherectomy can be the procedure of choice for young children with catastrophic epilepsies of diverse etiologies such as malformations of cortical development, Rasmussen’s encephalitis, Sturge-Weber syndrome, and remote vascular insults (Gonzalez-Martinez et al., 2005).

Palliative procedures

A. Corpus callosotomy

Corpus callosotomy (transection of the corpus callosum) is performed in a small number of patients, ie, those who have disabling seizures that rapidly become generalized or injurious drop attacks and are not candidates for focal resection. By disconnecting the two hemispheres, this procedure aims to
hinder the fast interhemispheric spread of seizure discharges 
(*Pati and Alexopoulos, 2010*).

Callosotomy may be complete or involve only a portion of the corpus callosum. The extent of resection has been correlated with favorable outcome (*Tanriverdi et al., 2009*).

Some investigators report a 50% or greater reduction in seizure frequency, with drop attacks and generalized tonic-clonic seizures showing the most consistent improvement. In addition, behavior and quality of life may also improve (*Asadi-Pooya et al., 2008*).

**B. Multiple subpial transections**

Multiple subpial transections are reserved for seizures arising from eloquent cortex (ie, from areas that cannot be removed without causing unacceptable neurologic deficits). Therefore, the surgeon only transects the epileptogenic cortex in a vertical manner, so as to interrupt the horizontal cortical connections without resection. This approach is thought to disrupt the synchrony of seizure propagation while preserving physiologic function (*Pati and Alexopoulos, 2010*).

A meta-analysis of small case series suggests some decrease in seizure frequency with no or minimal neurologic compromise in up to 60% of patients (*Spencer et al., 2002*).
Complications of epilepsy surgery

Resective surgery is not without risk, but often the risk is much less than that posed by uncontrolled epilepsy in the long term. Operative mortality rates vary from almost zero for temporal lobe surgery to 2.5% for hemispherectomy. The reported risk of permanent surgical morbidity varies by type of surgery from 1.1% for temporal lobe resection to about 5% for frontal lobe resection (Chapell et al., 2003).

Ketogenic diet

Originally developed almost a century ago, the diet mimics the biochemical changes associated with starvation. It is a strict regimen, high in fat and low in carbohydrate and protein (typically in a ratio of 4:1 or 3:1 in adolescents and very young children) (Pati and Alexopoulos, 2010).

Ketogenic diet is mainly used in pediatric patients (due to tolerability) as second line treatment in focal nonsurgical refractory and generalized symptomatic epilepsy. A recent randomized controlled trial showed a reduction in seizure frequency more than 50% in 38% of children with drug-resistant epilepsy (Neal et al., 2008).

Such a strict regimen is difficult to implement and maintain and requires close supervision by a dietician and physician. In addition to the practical complexities, concerns
also exist about the long-term effects of the diet on the child’s growth and overall health. For these reasons, the ketogenic diet is restricted to a small group of young patients with pharmacoresistant epilepsy and is not usually used long (Pati and Alexopoulos, 2010).

Potential adverse effects of the ketogenic diet include lethargy, weight loss, nausea and vomiting, constipation, and diarrhea. Furthermore, the diet’s use necessitates the frequent monitoring of complete blood count levels, electrolyte values, and liver and renal status, as additional infrequent adverse effects can include hyperlipidemia, hypoglycemia, hypocalcemia, electrolyte imbalances, and metabolic acidosis, in addition to cardiac and renal abnormalities (Olson, 2005).

There are few data indicating when it is appropriate to terminate the diet in patients who have a favorable response, but most clinicians wean the patient after 2 to 3 years. Reports on the use of the ketogenic diet in adults are scarce, although benefit was seen in a small series. No long-term follow-up data exist for adults, especially regarding the risk of atherosclerosis (Pati and Alexopoulos, 2010).
Vagus nerve stimulation

Vagus nerve stimulation is a nonpharmacologic alternative for adults and for adolescents over age 12 years who have intractable focal seizures and who are not favorable surgical candidates. Its effectiveness in younger patients and in those who have intractable generalized seizures is less clear (Holmes et al., 2004). It might also be effective in children with drop attacks and Lennox-Gastaut syndrome (Beleza, 2009).

A device consisting of a pulse generator is implanted subcutaneously in the precordium, and a lead wire is tunneled under the skin and attached to the left vagus nerve. The generator is programmed using a telemetry wand held over the device, with settings for current intensity (typically 1–2 mA), pulse width (250–300 μsec), frequency (30 Hz), and “duty cycle” (typically 30 seconds on stimulation, followed by 3 to 5 minutes off, cycling 24 hours/day). Hence, it provides “open-loop stimulation,” ie, continuous stimulation that is not modified in response to the patient’s EEG seizure activity. Patients or caregivers can also activate the device manually (“on demand”) at the first sign or warning of an impending seizure by swiping a handheld magnet (Pati and Alexopoulos, 2010).

Common side effects such as cough, voice alteration, and hoarseness are usually stimulation-dependent and tend to
diminish with time. Notably, vagus nerve stimulation has none of the cognitive side effects often encountered with increasing doses of antiepileptic drugs. As with other implantable stimulators, some safety concerns exist in patients undergoing magnetic resonance imaging (Pati and Alexopoulos, 2010).

At least one-third of patients who receive this treatment show a sustained response, defined as a 50% or greater reduction in seizures. However, few achieve freedom from seizures, and therefore this therapy is considered palliative and is reserved for patients who are not candidates for surgery or for whom surgery has failed (Pati and Alexopoulos, 2010).
**Treatments under investigation**

Polymers, electrical brain stimulation and prediction of seizures may be available in the future for treating patients with refractory epilepsy. Cell transplantation and gene therapy, although holding great promise, are still far from routine clinical use (*Nilsen and Cock, 2004*).

**Local drug delivery**

Polymers containing anti-epileptic drugs consist of 2- to 3-mm microspheres that might be placed near the epileptogenic zone. Advantages include: (1) new anti-epileptic drugs could be used including those which do not cross the blood-brain barrier or show systemic toxicity; (2) they may be useful when the epileptogenic zone is near eloquent cortex; (3) they prevent noncompliance (*Kwan and Brodie, 2006*).

Implanting wafers impregnated with chemotherapeutic agents into the resection cavity results in prolongation of survival without an increased incidence of adverse events (*Hart et al., 2008*).

**Targeted electrical stimulation**

To modulate abnormal cortical hyperexcitability, electrical stimulation can be applied to the peripheral nervous system (eg, vagus nerve stimulation) or central nervous system.
Central nervous system stimulation can be broadly divided into two approaches:

- **Direct stimulation** targets presumed epileptogenic brain tissue such as the neocortex or hippocampus.
- **Indirect stimulation** targets presumed seizure-gating networks such as in the cerebellum and various deep brain nuclei in the basal ganglia or thalamus (*deep brain stimulation*), which are believed to play a central role in modulating the synchronization and propagation of seizure activity (*Pati and Alexopoulos, 2010*).

Electrical brain stimulation is still not accepted as a routine treatment for epilepsy, partly because there is no consensus regarding the better region to stimulate and in what type of seizure it is most effective. The epileptogenic zone and the centromedian or anterior nuclei of the thalamus seem to be the most effective targets for electrical stimulation. The efficacy seems to be similar to vagal nerve stimulation which has a lower risk and less comorbidity. This intervention is thus unlikely to be routinely used in the future (*Beleza, 2009*).

**Cell and gene therapies**

In ex vivo gene therapy, bioengineered cells capable of delivering anticonvulsant compounds might be transplanted into specific areas of the brain. On the other hand, in vivo gene
therapy would involve delivering genes by viral vectors to induce the localized production of antiepileptic compounds in situ. Cell transplantation is aimed at restoring the physiologic balance of neurotransmitters. Cell transplantation (heterologous fetal cell grafts or embryonic or adult stem cells) has the potential to form restorative synaptic connections and assimilate within existing cells and networks in the host tissue (Pati and Alexopoulos, 2010).
DISCUSSION

Epilepsy is a common and devastating neurological disorder. In many patients with epilepsy, seizures are well-controlled with currently available anti-epileptic drugs, but a substantial proportion (about 30%) of patients continue to have seizures despite carefully optimized drug treatment (Remy and Beck, 2006).

Firstly it is mandatory to exclude false refractoriness related to nonepileptic seizures, inadequate anti-epileptic drugs, noncompliance and seizure-precipitating factors. Video-EEG monitoring is an essential tool in this process, aiming to perform a differential diagnosis of paroxysmal events and a correct classification of seizures and epileptic syndromes (Beleza, 2009).

An important characteristic of medically intractable (pharmaco-resistant) epilepsy is that most patients with refractory epilepsy are resistant to several, if not all anti-epileptic drugs, even though these drugs act by different mechanisms (Kwan and Brodie, 2000).

Although no single accepted definition exists of drug resistant epilepsy, different definitions have been proposed depending on the context. All are based on the 3 main
components of intractability: number of anti-epileptic drugs previously taken, frequency of seizures and duration of non-controlled epilepsy (Beleza, 2009).

In general, many experts would agree that whenever a patient does not become seizure free for 12 months during long-term treatment with several suitable anti-epileptic drugs at maximal tolerated doses, the epilepsy can be broadly classified as drug-resistant, pharmaco-resistant, or medically refractory (Schmidt and Loscher, 2005).

Refractory epilepsy is established when there is inadequate seizure control despite using potentially effective anti-epileptic drugs at tolerable levels for 1-2 years, and excluding non-epileptic events and poor compliance (Beleza, 2009).

Two main hypotheses have been proposed to account for Pharmacoresistant epilepsy. The transporter hypothesis states that pharmaco-resistance arises because anti-epileptic drugs do not gain access to their sites of action in the brain because of over-expression of drug efflux transporters at the blood brain barrier that limit anti-epileptic drug access to the brain. The target hypothesis, on the other hand, states that target receptor sites are somehow altered in the epileptic brain so that they are much less sensitive to the anticonvulsant effects of systemically administered drugs (Beck, 2007).
The transporter and target hypotheses are the most commonly cited mechanisms of refractoriness, although they cannot yet fully explain refractoriness (Beleza, 2009).

Transporter hypothesis is based on two separate but parallel assumptions. First, increased expression of drug transporters is associated with refractory epilepsy. Second, anti-epileptic drugs are substrates of these transporters. Otherwise, over-expression of the transporters would have no clinical relevance (Kwan and Brodie, 2005).

According to the drug transporter hypothesis, restricted access of anti-epileptic drugs to the seizure focus is the result of locally increased expression of drug transporter proteins, most notably P-gp, encoded by the ABCB1 gene (Beleza, 2009).

A number of drug transporter genes and their proteins are over-expressed in the blood brain barrier of individuals with refractory epilepsy. This has been demonstrated in tissues taken from epileptic foci at the time of resective surgery (Dombrowski et al., 2001).

In various pathologies commonly associated with drug-resistant epilepsy, upregulation of P-gp has been noted in brain capillary endothelium, consistent with the putative enhanced blood brain barrier function. It has been postulated that this might represent an adaptive phenomenon contributing to cell
survival, but its relevance to drug resistance is unclear. It is likely that the specific cell-distribution patterns of these efflux transporters serve different cellular functions, which remain to be fully illuminated (Kwan and Brodie, 2005).

Evidence to support the assumption that increased expression of drug transporters is associated with refractory epilepsy has mainly been derived from epileptic brain tissues removed during epilepsy surgery from patients with drug resistant epilepsy. Interpretation of findings from surgical studies can be difficult because of the lack of proper normal controls for comparison (Kwan and Brodie, 2005).

The proposed mechanism suffers from a lack of evidence that many clinically used anti-epileptic drugs are substrates for human P-gp or any other known human blood brain barrier efflux transporter (Anderson and Shen, 2007).

Although an impression is emerging that several anti-epileptic drugs may be subject to active transport by P-gp or MRP, inconsistencies in experimental findings exist, likely reflecting the methodologic differences used by different investigators. Further studies using more specific and sensitive models are needed before conclusive identification of anti-epileptic drugs as substrates of the various transporters can be made (Kwan and Brodie, 2005).
The transporter hypothesis has also failed to receive support from recent genetic studies that failed to report an association between polymorphisms in the \textit{ABCB1} gene and drug resistance \cite{Leschziner2007}.

Findings from several animal models suggest that P-gp expression could be induced by seizures or treatment with certain anti-epileptic drugs. Whether this induction effect can be applied to the human situation is unknown and requires further investigation \cite{KwanBrodie2005}.

There is as yet no direct proof that over-expression of multidrug transporters is a possible cause of drug resistance in the treatment of epilepsy. In addition, other mechanisms of pharmacoresistance should be identified, because it is likely that different factors underlie multidrug resistance in epilepsy \cite{LoscherPotschka2002}.

According to the target hypothesis, epilepsy pharmacoresistance occurs when intrinsic or acquired changes in drug targets make them less sensitive to anti-epileptic drugs. Recent studies have provided evidence of reduced sensitivity to carbamazepine in brain tissue from patients who were clinically unresponsive to carbamazepine and underwent resective surgery. However, it is unknown whether pharmacodynamic insensitivity in these tissues extended to anti-epileptic drugs.
with different mechanisms of action or even to other anti-epileptic drugs that target sodium channels (Beleza, 2009).

The acquired version of the target hypothesis proposes that the pharmacodynamic sensitivity of the anti-epileptic drug target is modified by the disease state (Lazarowski et al., 2007). There are many examples of changes in the activity of voltage-gated and neurotransmitter-activated ion channels in acquired epilepsy models, some of which lead to reduced responsiveness to anti-epileptic drugs (Remy and Beck, 2006). However, there is no evidence that the efficacy of anti-epileptic drugs acting on different targets is similarly affected (Beleza, 2009).

It seems highly unlikely that multiple targets will all be simultaneously altered in such away as to produce pharmacoresistance. This should be kept in mind when considering the target hypothesis for most anti-epileptic drugs (Beck, 2007).

An alternative mechanism for explaining refractoriness was suggested “the intrinsic disease severity”. This hypothesis claims that there are differences in inherent epilepsy severity reflected in the frequency of seizures in the early phase of epilepsy. Possibly, common neurobiological factors may underlie both epilepsy severity and drug refractoriness. Subsequently, to advance in the understanding and therapeutic management of refractory epilepsy, it is crucial to identify
biomarkers which define the most severe forms of epilepsy. Unfortunately, there are few studies on the contribution of genetics to the severity of epilepsy (Beleza, 2009).

Malformations of cortical development are often associated with severe epilepsy and developmental delay. About 40% of drug-resistant epilepsies are caused by malformations of cortical development. Classification of malformations of cortical development is based on embryological brain development, recognizing forms that result from faulty neuronal proliferation, neuronal migration and cortical organization (Guerrini et al., 2003).

Studies of different malformations of cortical development with abnormal glioneuronal proliferation, such as tuberous sclerosis complex, focal cortical dysplasia, and ganglioglioma, share some interesting trends regarding the site of origin for seizures. Both the lesion and the perilesional regions have been implicated in causing epileptogenesis in these disorders, but, somewhat paradoxically, an accumulating amount of evidence demonstrates the importance of perilesional cortex in producing seizures. It is likely that the relative contribution of perilesional versus lesional mechanisms varies between different types of malformations of cortical development and different patients with the same type of malformations of cortical development. Recent studies suggest that the “perilesional” region may have
subtle structural and cellular abnormalities. With further advances in mechanistic studies and improved resolution of imaging techniques, future research should reveal more detailed information about the perilesional region and its relationship to the lesion (Wong, 2008).

There was over-expression of both P-gp and MRP1 in reactive astrocytes in the epileptogenic tissue in dysembryoplastic neuroepithelial tumors, focal cortical dysplasia and hippocampal sclerosis, and MRP1 over-expression in dysplastic neurons in focal cortical dysplasia (Sisodiya et al., 2002).

As the clinically practical definition of “lesion” is currently limited to the anatomical resolution of imaging methods, future advances will likely result in continual expansion of the definition and extent of the epileptogenic “lesion” from the anatomical to the cellular and molecular levels, so that the present distinction between “lesion” and “perilesional” regions may become obsolete (Wong, 2008).

The chances of controlling epilepsy decline sharply after failure of the second or third antiepileptic drug trial. In fact, some clinicians would argue against trying another antiepileptic drug in these patients, who may be candidates for surgical procedures that have high rates of success (Berg, 2004).
Defining epilepsy refractory to medical treatment implies considering surgery. The prognosis will differ according to the epilepsy syndrome and etiology involved and depending on whether the intervention is curative or palliative. In addition, other interventions such as a ketogenic diet and the contribution of anti-epileptic drugs should not be disregarded (Beleza, 2009).

The ketogenic diet, which was developed almost a century ago, controls seizure activity by a mechanism that has not yet been identified. The dietary changes involved are complicated and require extensive family commitment, but they may be extremely effective in seizure reduction. The diet includes 80% to 90% of calories from fat, protein appropriate for growth, and extreme carbohydrate restriction; the diet typically is more successful with younger children in whom diet is easily controlled by parents (Olson, 2005).

Such a strict regimen is difficult to implement and maintain and requires close supervision by a dietician and physician. In addition to the practical complexities, concerns also exist about the long-term effects of the diet on the child’s growth and overall health. For these reasons, the ketogenic diet is restricted to a small group of young patients with pharmacoresistant
epilepsy and is not usually used long (Pati and Alexopoulos, 2010).

Epilepsy surgery can be classified as curative or palliative, depending on the goal. Curative procedures include lobectomy, lesionectomy, and multilobar or hemispheric surgery (hemispherectomy). Palliative procedures, in contrast to curative ones, rarely eliminate seizures entirely. It is important to determine that patients are not candidates for a curative resective procedure before considering palliative surgical options such as corpus callosotomy, multiple subpial transections, or vagus nerve stimulation (Pati and Alexopoulos, 2010).

Operative mortality rates vary from almost zero for temporal lobe surgery to 2.5% for hemispherectomy. The reported risk of permanent surgical morbidity varies by type of surgery from 1.1% for temporal lobe resection to about 5% for frontal lobe resection (Chapell et al., 2003).

Polymers, electrical brain stimulation and prediction of seizures may be available in the future for treating patients with refractory epilepsy. Cell transplantation and gene therapy, although holding great promise, are still far from routine clinical use (Nilsen and Cock, 2004).
SUMMARY

In many patients with epilepsy, seizures are well-controlled with currently available anti-epileptic drugs, but a substantial proportion of patients continue to have seizures despite carefully optimized drug treatment.

Different definitions exist for drug resistant epilepsy. Definitions usually include number of anti-epileptic drug failures and seizure frequency in a specified duration of therapy.

Risk factors for refractoriness include early onset of seizures, high seizure frequency and certain structural abnormalities such as cortical dysplasia.

Refractory epilepsy is established when there is inadequate seizure control despite using potentially effective anti-epileptic drugs at tolerable levels for 1-2 years, and excluding non-epileptic events and poor compliance.

Two concepts have been put forward to explain the development of pharmacoresistance. The transporter hypothesis contends that the expression of multidrug transporters in the brain is augmented, leading to impaired access of anti-epileptic drugs to CNS targets. The target hypothesis states that
epilepsy-related changes in the properties of the drug targets themselves may result in reduced drug sensitivity.

According to transporter hypothesis, multidrug transporters are over-expressed in epileptogenic brain tissue and these transporters include P-gp and MRPs. This limits anti-epileptic drug access to drug targets.

Regarding target hypothesis, drug targets are modified structurally and/or functionally and this makes them less sensitive to anti-epileptic drugs. Reduced sensitivity of drug targets to anti-epileptic drugs has been suggested for the voltage-gated Na+ channel and the GABA_A receptor.

Certain structural abnormalities of the brain have been associated with drug resistant epilepsy. Of these abnormalities, malformations of cortical development have a prominent role and are often associated with severe epilepsy and about 40% of drug-resistant epilepsies are caused by malformations of cortical development. These malformations of cortical development include focal cortical dysplasia, periventricular nodular heterotopias, tuberous sclerosis complex, gangliogliomas and dysembryoplastic neuroepithelial tumors.

Surgery is considered when epilepsy is refractory to medical treatment. Surgery ranges from curative to palliative depending on the epilepsy syndrome and etiology. Curative
procedures include lobectomy, lesionectomy, and hemispherectomy. Palliative procedures include corpus callosotomy, multiple subpial transections and vagus nerve stimulation.
RECOMMENDATIONS

Future directions of research and experimental studies should address revealing more data about the following

- Evidence that the multidrug transporters regulate intraparenchymal concentrations of anti-epileptic drugs.
- Evidence that multidrug transporter expression and/or transporter function is upregulated in human and experimental epilepsy.
- Regarding drug targets, evidence should be available that drug targets are less sensitive to a given anti-epileptic drug in chronic epilepsy.
- Evidence that genetic or pharmacological manipulation of drug transporters/drug targets affects sensitivity to anti-epileptic drugs.
- In addition, data on human epilepsy patients should be obtained regarding Association of polymorphisms in drug transporter/drug target genes with clinical pharmacoresistance.
REFERENCES


الصرع المقاوم للعقاقير

رسالة مقدمة كتوطينة للحصول على درجة الماجستير في
فرع الأمراض العصبية والنفسية

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2010
المخاطب العربي

في العديد من مرضى الصرب يتم التحكم في النوبات الصرعية عن طريق العقاقير المضادة لصلاب. وبالرغم من ذلك فإن هذه النوبات تستمر في الحدوث في نسبة غير قليلة من هؤلاء المرضى.

هناك تعريفات مختلفة لتحديد مفهوم الصرب المقاوم للعقاقير وتشمل هذه التعريفات عادة عدد المرات التي لم يتم الاستجابة فيها للعقاقير أو مدى تكرار النوبات الصرعية خلال فترة محددة من العلاج.

عوامل الخطورة التي قد تؤدي إلى حدوث مقاومة للعقاقير تشمل الإصابة المبكرة بالصلاب وارتفاع وتيرة حدوث النوبات ووجود تشوهات هيكليّة معينة مثل النمو الشاذ للقشرة المخية.

بعد الصرب مقاومة للعقاقير إذا لم يحدث استجابة كافية بالرغم من استخدام عقاقير مؤثرة بمستويات مقبولة لمدة تتراوح من سنة إلى سنتين.

هناك فرضيتين تم تقديمهما لتصفية مقاومة العقاقير في مرضى الصرب. تقوم فرضية النواقل على عدم إمكانية وصول العقاقير إلى مستقبلاتها نتيجة الزيادة في نواقل هذه العقاقير. بينما تقوم فرضية المستقبلات على وجود تغيرات في المستقبلات هذه العقاقير مما يؤدي إلى نقص حساسيتها للعقاقير المستخدمة.

وفقاً لفرضية الفرصة الخاصة بنواقل العقاقير فإنها تشير إلى زيادة مستويات هذه النواقل في النسب الصعب و هذه النواقل تشمل MRPs و P-gp وهذا يحدد من وصول العقاقير إلى المستقبلات.

أما بالنسبة لفرضية الفرصة الخاصة بمستقبلات العقاقير فإنها تقوم على وجود تغيرات تركيبية أو وظيفية في هذه المستقبلات تؤدي إلى نقص حساسيتها للعقاقير ويرجح حدوث ذلك مع قنوات الصوديوم ومستقبلات GABA_A.
وقد ارتبطت تشبهات هيكليّة معينة في المخ بالصرع المقاوم للعقاقير و يأتي على رأسها تشبهات نمو القشرة المخية والتي غالبا ما يصاحبها الصرع الشديد. حوالي 40% من حالات الصرع المقاوم للعقاقير يكون سببها تشبهات نمو القشرة المخية و تشمل هذه التشبهات focal cortical dysplasia و periventricular nodular heterotopias و tuberous sclerosis complex و gangliogliomas و dysembryoplastic neuroepithelial tumors و gangliogliomas.

تؤخذ الجراحة في الاعتبار عندما يكون الصرع مقاوما للعلاج الدوائي و تتراوح الجراحات من جراحة علاجية إلى جراحة مرتفعة اعتبارا على أعراض lesionectomy و lobectomy و lesionectomy. تشمل الجراحات العلاجية و تشمل الجراحات المرتفعة corpus callosotomy و hemispherectomy و vagus nerve stimulation و multiple subpial transections.