

Mechanisms of Pharmacoresistance to Anti- epileptic Drugs

Terence O'Brien
Christian Elger

Pharmacoresistance in Epilepsy

- No universally agreed definition
- Continued occurrence of seizures despite maximum tolerated doses of 3 appropriate AEDs.*
 - Not related to:
 - Medication non-compliance.
 - Significant provoking factors.
 - Inappropriate drug or doses.
 - Progressive neurological disease.

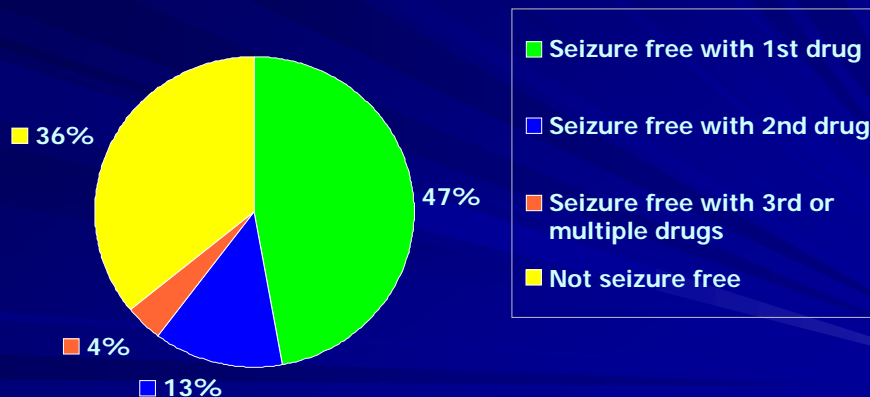
*Arroyo et al., Epilepsia 2002;43:437-444.

Pharmacoresistance in Epilepsy

- Common:
 - Up to 40% of patients.
- Broad spectrum
 - If resistant to one AEDs, highly likely to resistant to all AEDs.
- Major health and socioeconomic burden.
- New AED have made little inroads.
- Mechanisms still poorly understood.

Outcomes of Epilepsy Drug Treatment

Previously Untreated Epilepsy Patients (N=470)



Kwan P, Brodie MJ. *N Engl J Med.* 2000;342(5):314-319.

Clinical Factors Predictive of Pharmacoresistant Epilepsy

- Symptomatic or cryptogenic epilepsy
- Early age of onset
 - <1 yr.
- Higher number of seizures prior to treatment
 - but early treatment NOT protective
- Failure of control with first AED
- EEG:
 - Focal epileptiform discharges
 - Generalised slowing
- MRI lesion
 - MTS, disorders of cortical development.

Limited usefulness in individual patients

Clinical Factors NOT Predictive of Pharmacoresistant Epilepsy

- Early treatment^{1,2}.
- Type of AED used first.
 - Outcome with “older” AED = with “new” AED.

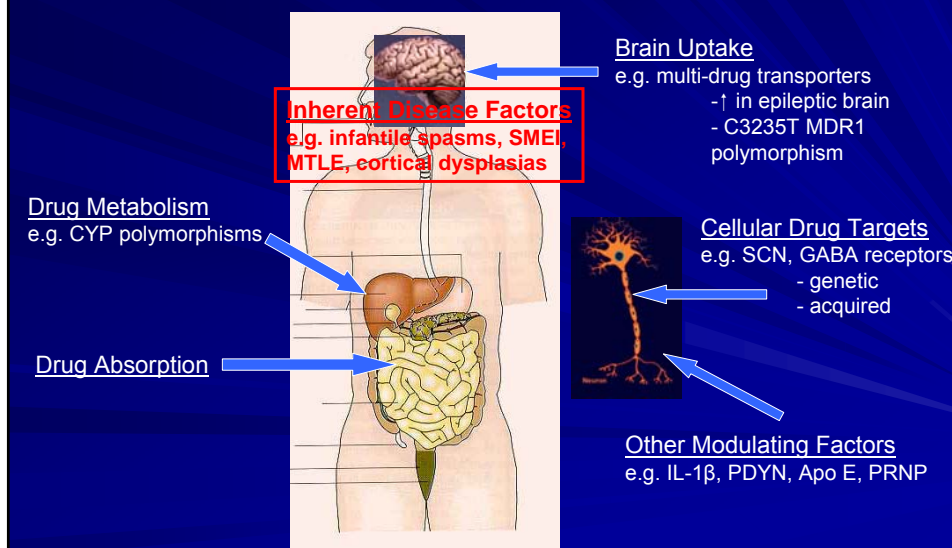
¹ Musicco M, et al. Neurology 1997;49:991-8.

² Camfield C, et al. Neurology 1996;46:41-4.

Consequences of Pharmacoresistant Epilepsy

- Increased AED side-effects from long-term high dose polytherapy
- Mortality twice that of the general population
- Accidental injuries
- Psychosocial Impact
 - Driving, work & family
 - Reduced quality of life
 - Higher depression rates
- Memory impairment
 - ? Cognitive impairment
- High direct and indirect economic cost¹

Possible Sites for Pharmacoresistance

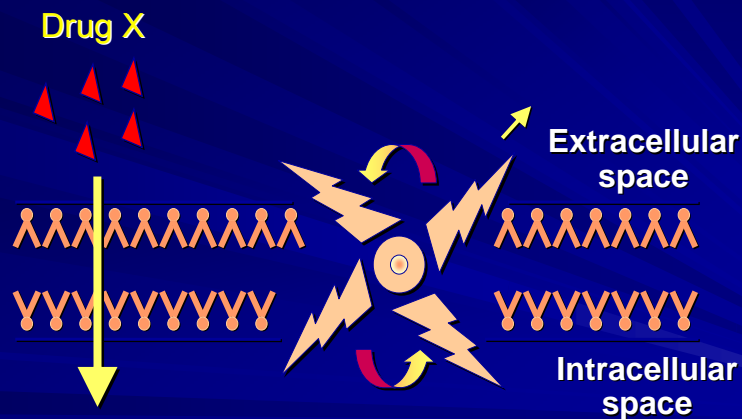


Currently Available AEDs

- Phenytoin
- Carbamazepine
- Valproic acid
- Phenobarbitone
- Ethosuximide
- Primidone
- Clonazepam
- Gabapentin
- Lamotrigine
- Topiramate
- Gabapentin
- Tiagabine
- Vigabatrin
- Clobazam
- Leviteracetam
- Pregabalin

*Resistance to one AED highly predictive
or resistance to all AEDs
= BROADSPECTRUM MECHANISMS*

Multidrug Transporters



Courtesy P. Kwan

Multi-drug Membrane Transporters

- Majority adenosine triphosphate-binding cassette (ABC) proteins
 - ATP-driven pumps transporting a range of substrates
- P-Glycoprotein (P-gp/MDR1) (ABCB1) is best known
 - MRP1 (ABCC1)
 - MRP2 (ABCC2)
 - Many others (>50, seven subfamilies)
- Level of drug resistance in transfected cells correlates with density of P-gp on cell surface
- Cancer patients, presence in tumour cells associated with poor prognosis, absence with good prognosis.

Choi K et al, Cancer Chemother Pharmacol 1997;40(suppl):S3-8.
Silverman JA. Pharmaceut Biotech 1999;12:353-86

Drug Transporters & AED Resistance: Necessary requirements

1. Anti-epileptic drugs are transporter substrates
2. Transporters are over-expressed in drug resistant epilepsy
3. Over-expression results in resistance to seizure control from AEDs.
4. Inhibition of transporter function restores anti-seizure effect of AEDs.
5. Relationship of genetic polymorphism with AED response.

Evidence that AEDs Functional Substrates for Drug Transporters

- Decreased brain accumulation of AED in mice with gene for transporters knocked out
 - P-GP – PHT, TPM
 - MRP2 – PHT
 - Not for CBZ.
- Inhibition of transporters (esp. P-gp) decreases brain accumulation
 - PHT, PB, LTG, FB, CBZ
- Evidence conflicting for CBZ
- Many transporters not yet studied

Over-Expression in Drug Resistant Epilepsy

Pathology	Cell type		
	Endothelium	Astrocytes	Neurones
Hippocampal sclerosis	P-gp, MRP2	P-gp, MRP1, MRP2	P-gp, MRP1
Focal cortical dysplasia	P-gp	P-gp, MRP1	P-gp, MRP1 (dysplastic neurones)
Tuberous sclerosis	P-gp	P-gp, ? MRP1	P-gp, MRP1
DNET	--	P-gp, MRP	--
Ganglioglioma	Pg-p	MRP1	P-gp, MRP1

Tishler DM et al, 1995; Drombowski SM et al, 2001; Sisodiya SM et al, 2001; Sisodiya SM et al, 2002; Aronica E et al, 2003; Aronica E et al, 2004

Is *MDR1* SNP Associated with Refractory Epilepsy? All Syndromes, England

Phenotype	Total	<i>MDR1</i> 3435 Genotype (%)		
	No.	CC	CT	TT
Drug-resistant	200	27.5%	53.0%	19.5%
Drug-responsive	115	15.7%	54.8%	29.6%
Non-epileptic control	200	18.5%	58.0%	23.5%

P<0.05

Siddiqui A et al, N Engl J Med 2003;348:1442-8

Is *MDR1* SNP Associated with Refractory Epilepsy? All Syndromes, Australia

MDR1 3435 Genotype (%)

Phenotype	Total	<i>MDR1</i> 3435 Genotype (%)		
	No.	CC	CT	TT
Drug-resistant	401	18.7%	48.1%	33.2%
Drug-responsive	208	17.8%	55.3%	26.9%

p=0.21

Tan NCK et al, Neurology 2004;63:1090-2

Drug Transporters & AED Resistance: Necessary requirements

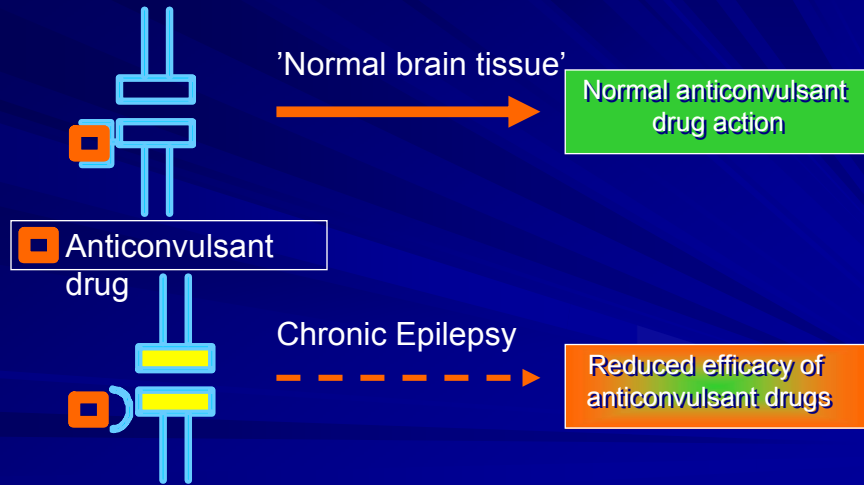
1. Anti-epileptic drugs are transporter substrates: ?
2. Transporters are over-expressed in drug resistant epilepsy: ✓
3. Over-expression results in resistance to seizure control from AEDs. ✓
4. Inhibition of transporter function restores anti-seizure effect of AEDs. ✓
5. Relationship of genetic polymorphism with AED response. ?

Alterations in Cellular Drug Targets

- Acquired
- Genetic

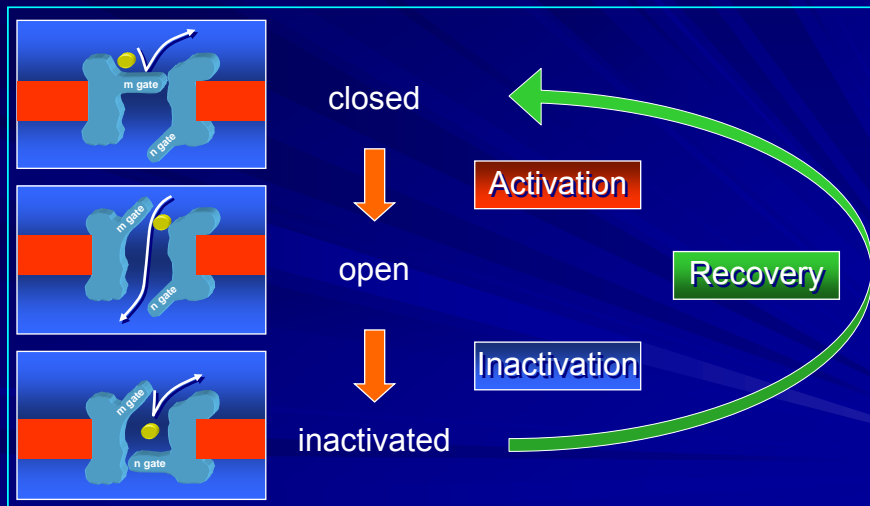
Pharmacoresistance

- Altered Pharmacosensitivity of Drug Targets - **Hypotheses**



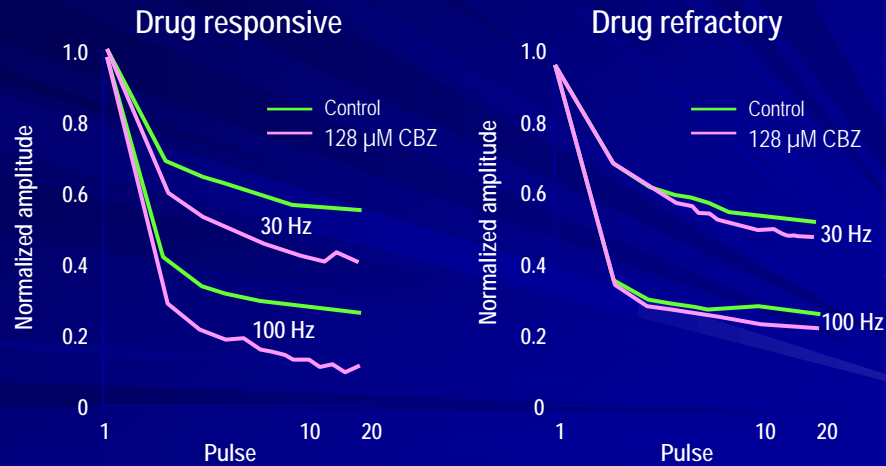
Analysis of Voltage-gated Sodium Channels

- Kinetic Scheme of Activation and Inactivation -



Loss of Use-Dependent Block by CBZ

Effect of **CBZ** on Na⁺ currents in human dentate granule cells



Remy S et al. Ann Neurol 2003;53:469-79

Genetic Polymorphism - SCN1

- Polymorphism SCN1A (SNP7 G>A) of this gene

– associated with increased maximal doses of **CBZ** in a chronic epilepsy population.

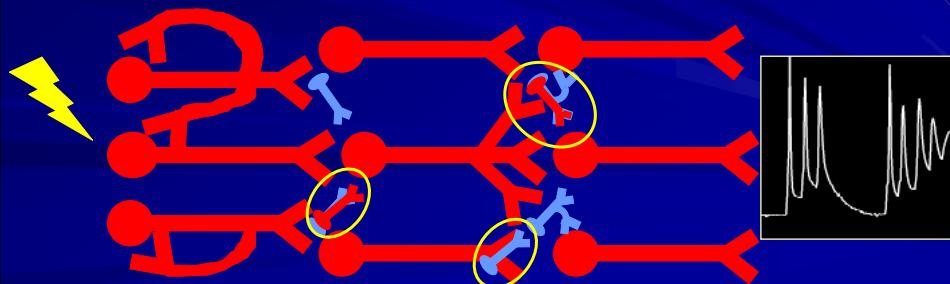
Tate et al, Proc Nat Acad Sci, 2005.

Inherent Disease Factors

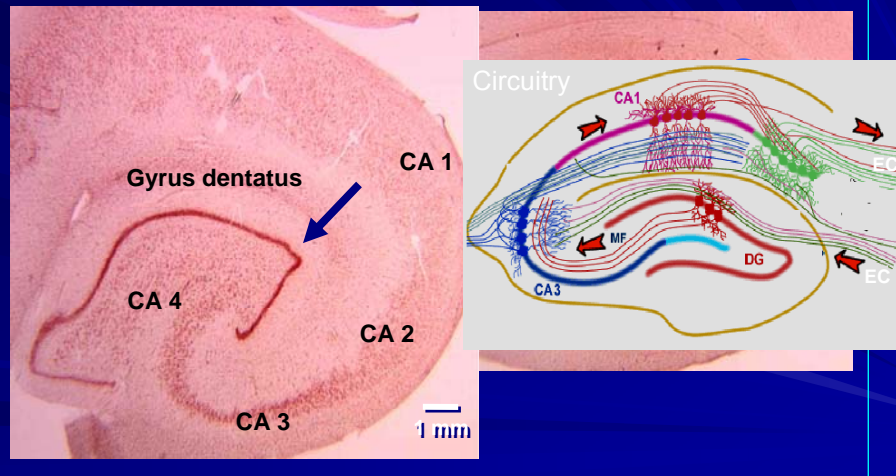
1. Increased epileptogenicity by neuronal network modifications.
2. Increased epileptogenicity by neuronal modifications.

Pharmacoresistance From Network Modifications

- Neuronal loss
 - Loss of inhibitory neurons
 - Loss of excitatory neurons
- Aberrant axonal sprouting
- Neurogenesis

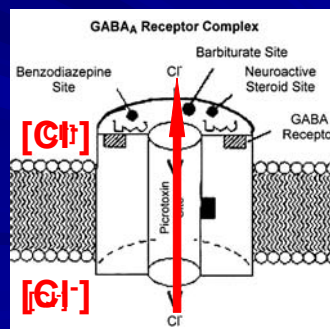


Network Modifications: Hippocampal Sclerosis



Changes in GABA Function

- Decreased expression of receptors
- Alterations in subunits
- Reversal of chloride potential*
 - GABA “excitatory”



*Cogen et al, Science 2002

Mechanisms for AED Pharmacoresistance: Conclusions

- AED pharmacoresistance is a common and important clinical problem.
- Patients resistant to one drug tend to be resistant to all drugs
 - despite their varied chemical structure, pharmacokinetics and pharmacodynamic properties.
- Mechanisms still uncertain, but likely to be broadly applicable across drug types
 - Multiple different mechanisms may contribute, including alterations in drug transport, site of action and inherent disease factors