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Causes and Mechanism of Drug-Resistant Epilepsy

Drug-Resistant Epilepsy (DRE)

Causes
&
Predictors

Mechanisms
&
Clinical suggestions

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DRE: Cause ?

DRE from ?

Pseudoresistance

- Wrong diagnosis: syncope, arrhythmia, PNES
- Wrong drug: not appropriate with seizure type
- Wrong dose: too low dosage
- Poor compliance / drug abuse

True DRE

Wrong diagnosis: most common

- Vasovagal syncope
- Cardiac arrhythmias
- Metabolic disturbances
- Psychogenic non-epileptic seizure
- Other neurologic disorders with episodic manifestations:
  - transient ischemic attacks
  - migraine

Wrong AED

- PHT, CBZ, oxcarbazepine, gabapentin, pregabalin, vigabatrin can worsen absence and myoclonic seizures
- Lamotrigine can also exacerbate some myoclonic epilepsy syndromes

Seizure Type /Syndrome	CBZ	OXC	PHT	LTG	VPA	GBP	VGB
Absences	+++	+	+++		+	+	++
Myoclonic	+++	+	+++	+		+	+
JME	++	+	++	+			
LGS/MAE	++	+	++	+		+	++
BECTS	++			+	+		
SMEI	+			++			+
LKS/ESES	+		+				

Sazgar and Bourgeois. Aggravation of epilepsy by antiepileptic drugs. Pediatr Neurol 2005

Aggravation by AEDs

Seizure / Epilepsy	PHT	CBZ	OXC	GBP	LTG	VGB
Absence sz	✓	✓	✓	✓		✓
Myoclonic sz	✓	✓	✓	✓		✓
JME	✓	✓	✓		✓	
LGS	✓	✓	✓	✓		✓
BRE		✓			✓	
Dravet syndrome	✓	✓			✓	✓

DRE: common cause

- Focal (structural) epilepsy
  - Focal cortical dysplasia
  - Hippocampal sclerosis
  - Dual pathologies
- LGS
- Dravet syndrome
- West syndrome
- Epileptic encephalopathy (EIEE, EME)
- Others: Ring chromosome 20

DRE: predictors of AED resistance

- Initial response to AED
- Underlying cause
  - Structural cause > genetic (idiopathic epilepsy syndrome)
  - Non-acquired cause (stroke, tumor, vascular malformation)
- High frequency of pre-AED seizure (> 10 seizures)
- Seizure clustering
- ? Early age of onset, status epilepticus?
- These factors are useful in only some, Not all, patient

French. Refractory epilepsy: clinical overview. Epilepsia. 2007
Tang et al. Drug-resistant epilepsy. Frontiers in Neurology. 2017

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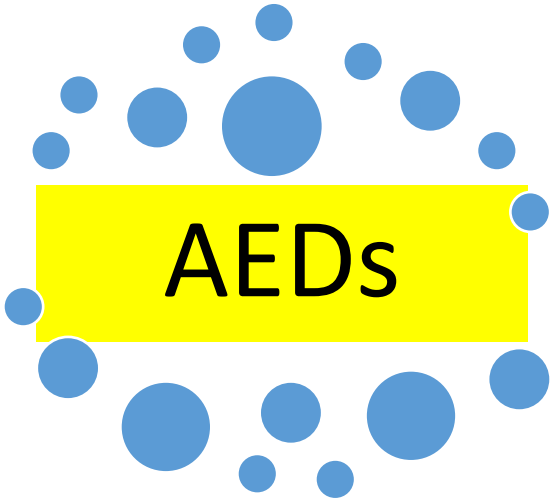
DRE: Mechanism ?

DRE: mechanism

- Variable
- Multifactorial
- Several proposed mechanisms
- Stand-alone theory ??

Any clinical or treatment suggestion ?

DRE: possible mechanisms



Targets

Access / Transport

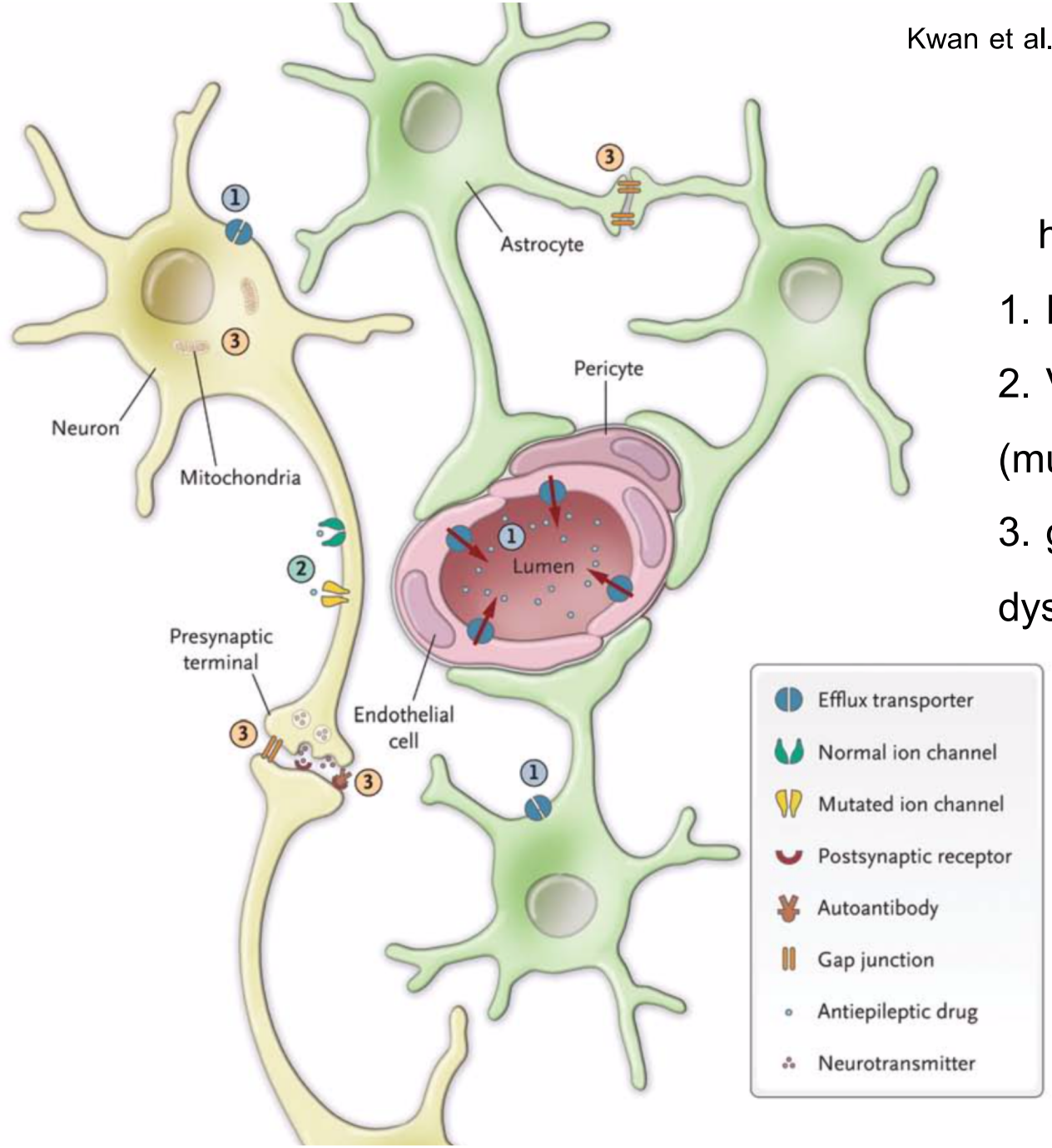
Alteration

DRE: Mechanisms

- Transporter hypothesis
  - Failure of drugs to reach their targets
- Alteration of drug target
- Drug missing the real target

Kwan et al. Current concepts: drug-resistant epilepsy. NEJM 2011

Kwan et al. Current concept DRE. NEJM 2011



Molecular locations of hypothesized mechanisms

1. Efflux Transporter (over)
2. Voltage-gated ion channels (mutated AED target)
3. gap junctions, mitochondrial dysfunction (new target)

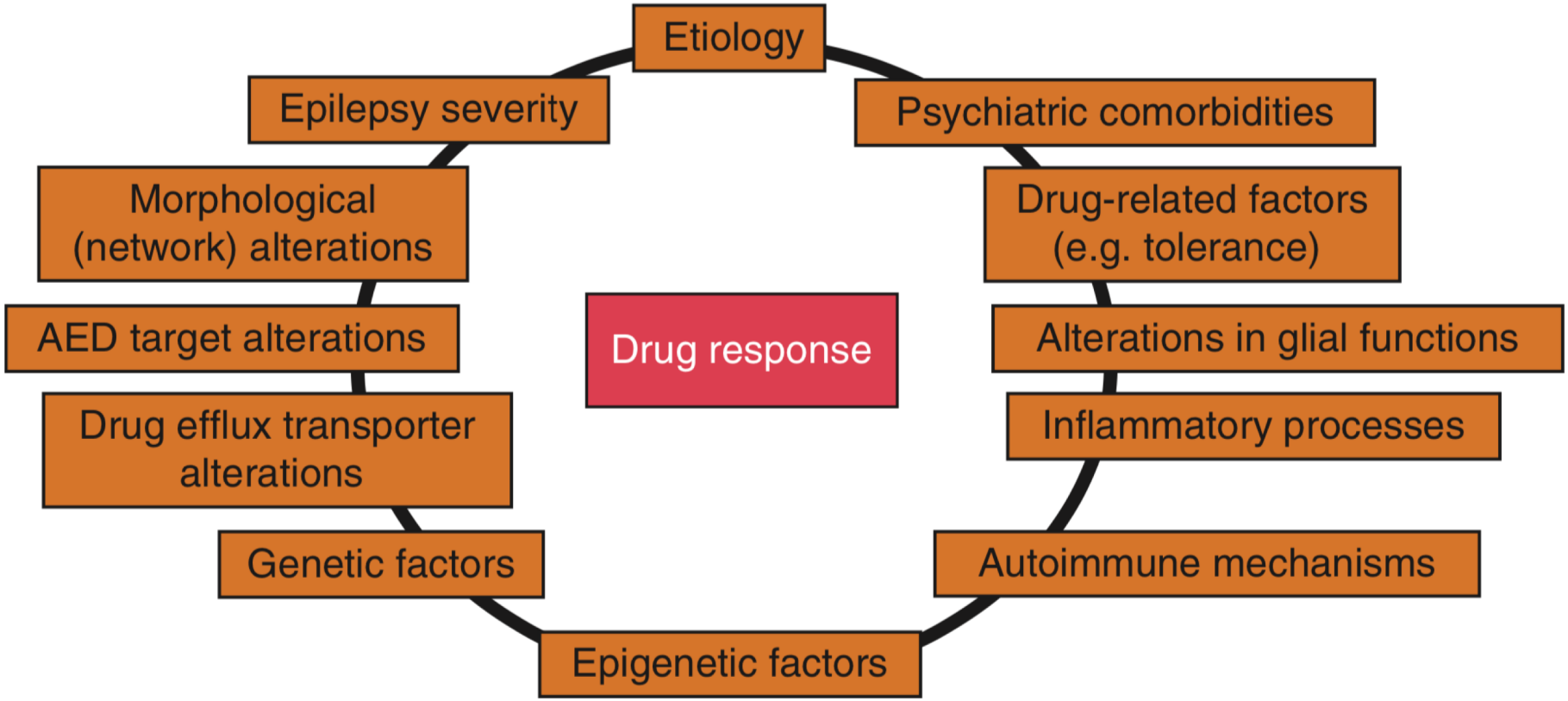
DRE: Mechanisms

- Transporter hypothesis
  - Failure of drugs to reach their targets
- Alteration of drug target
- Drug missing the real target

Kwan et al. Current concepts: drug-resistant epilepsy. NEJM 2011

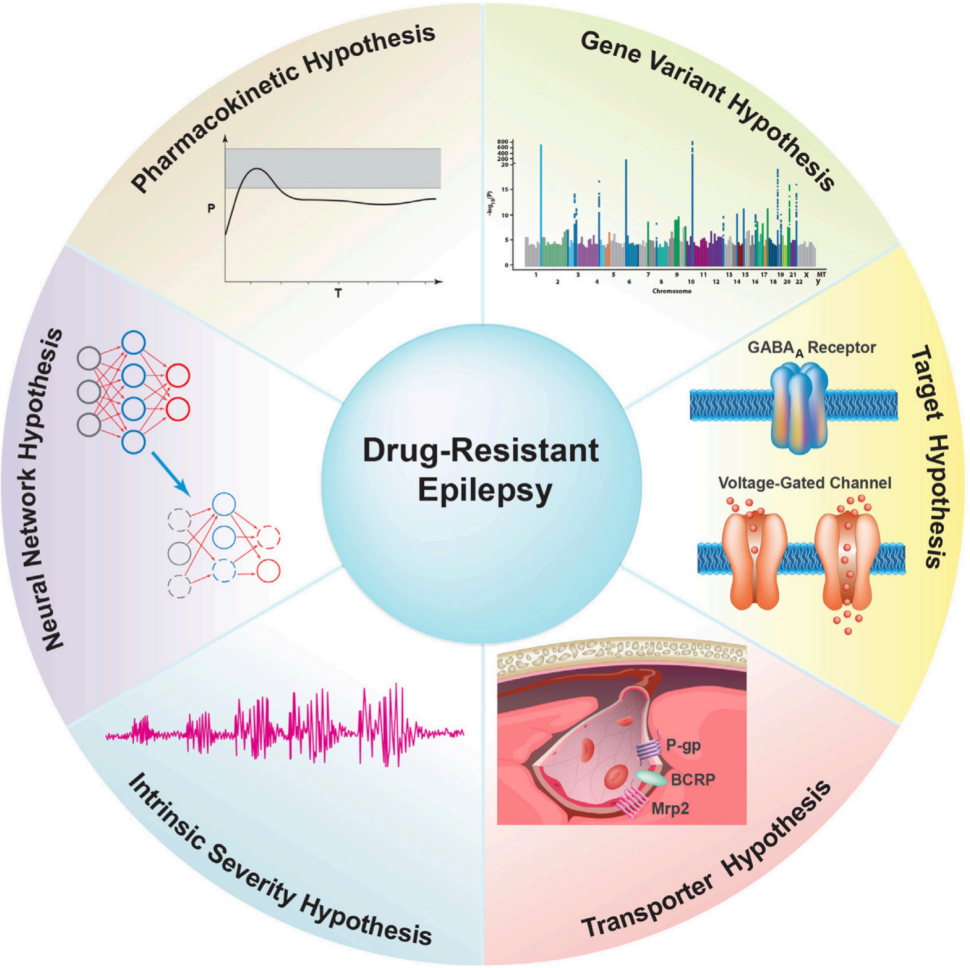
- Access of AEDs to their molecular targets in the brain
- Actions of the AEDs on their targets

Possible mechanisms of drug resistance in epilepsy



Löscher and Schmidt. Mechanism of drug resistant and tolerance. In: Shorvon S, Perucca E, Engel JJ, eds. The Treatment of Epilepsy. 4th ed. Wiley-Blackwell; 2016

Proposed hypothesis for mechanism of DRE



Tang et al. Drug-resistant epilepsy. Frontiers in Neurology. 2017

Pharmacokinetic hypothesis

- Overexpression of drug efflux transporters in peripheral organs (liver, intestine)
- Subtherapeutic AED level
- Reducing the amount of AED available to enter the brain

Based on case reports

- Low plasma PHT, CBZ level associated with overexpression of P-glycoprotein (P-gp) or other efflux transporters in liver or intestine

Pharmacokinetic hypothesis

- This hypothesis is likely not stand alone
- Therapeutic AED level vary among patients
- No one specific therapeutic AED level range is applicable to all patients

Clinical suggestion

➢ Should adjust AED dosage on an individual basis than to strictly rely on reference therapeutic AED level

Schmidt and Haenel. *Neurology* 1984
Johannessen et al. Ther Drug Monit 2003

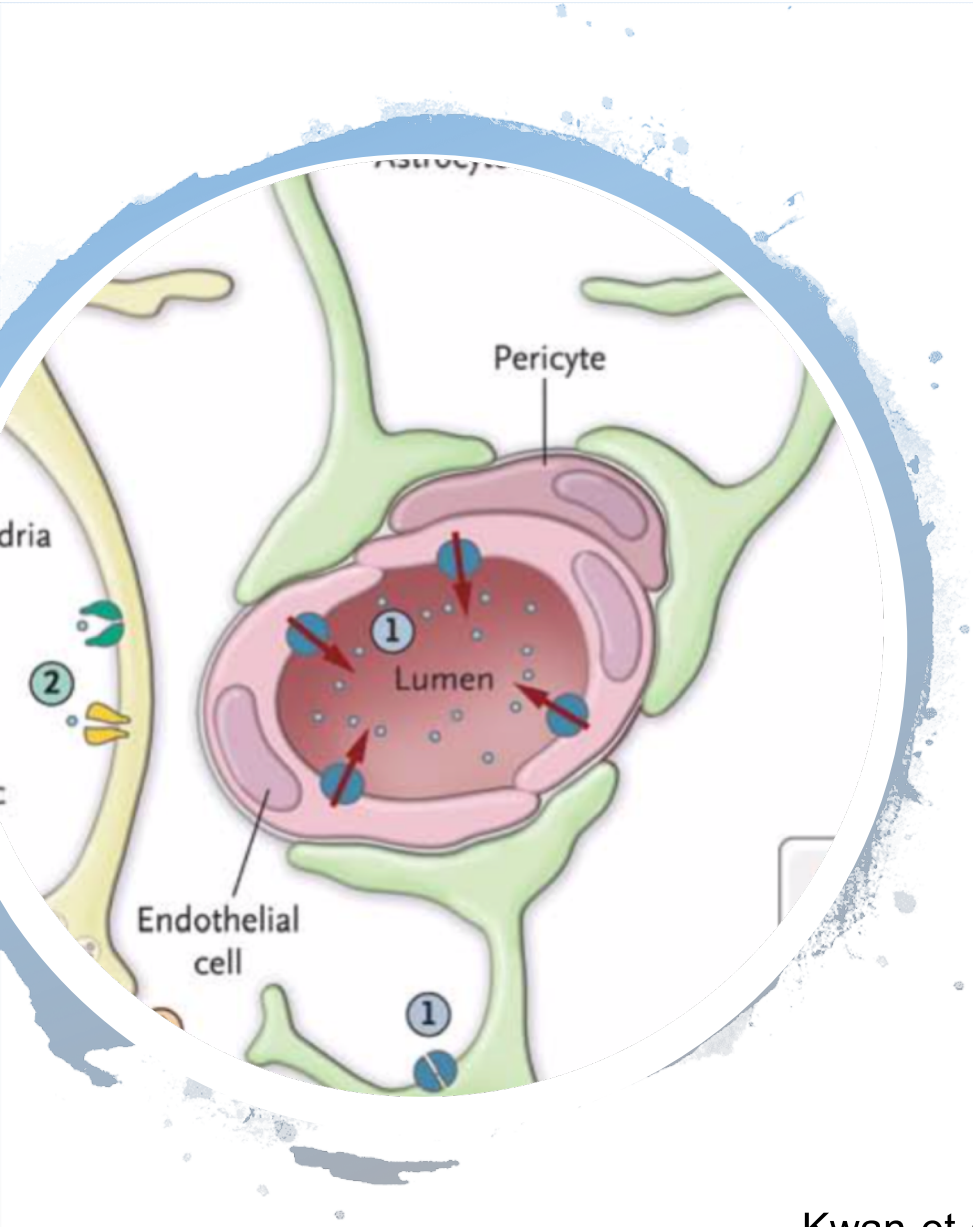
Transporter hypothesis

- Overexpression of AED efflux transporters at the blood–brain barrier
- Decreased AED brain uptake leading to resistance

- Multidrug resistance protein 1 (MDR1) or P-gp (later named) overexpressed in brain tissue resected from patients with refractory epilepsy

Tishler et al. Epilepsia 1995

- Multidrug Resistance-Associated Proteins (MRPs)



Overexpression of AED efflux transporters at brain capillary endothelium

Kwan et al. Current concept DRE. NEJM 2011

Transporter hypothesis

- Found in several studies both *in vivo* and *in vitro*
- AED transported by P-gp (definite)
  - Lamotrigine, oxcarbazepine, phenobarbital, and phenytoin

Zhang et al. The transport of antiepileptic drugs by P-gp. *Adv Drug Deliv Rev* 2012

- AED transported by MRPs (possible)
  - Phenytoin, CBZ, VPA
- Caused by both genetic factor and recurring seizure

Transporter hypothesis

- Two main mechanisms for this hypothesis

1. AED-mediated induction of efflux transporters *via* nuclear receptors
2. Recurring seizure-induced signaling causing efflux transporter overexpression

Potential treatment strategy

➢ P-gp inhibitor: directly inhibiting the efflux transporters

Palmeira et al. *Curr Med Chem* 2012

P-gp inhibitor generations

1. Non-specific P-gp inhibitors such as cyclosporine A and verapamil
2. Cyclosporine A analog: more specific to P-gp but interfere with CYP3A4
3. P-gp specific inhibitor

Low-dose verapamil (20 mg three times daily) as adjunctive treatment in refractory epilepsy

- 10 out of 19 patients achieved 50% or more sz reduction
- None have CVS or hemodynamic adverse events

Narayanan et al. Low dose verapamil as an adjunct therapy for medically refractory epilepsy an open label pilot study. Epilepsy Res 2016

Target hypothesis

- Alteration in the property of AED targets
- Change in voltage-gated ion channels (Na channel) and neurotransmitter receptors ($GABA_A$ receptor)
- Decreased drug sensitivity leading to resistance

Target hypothesis

- Loss of (use-dependent) blockage of Na channels in dentate granule cells by CBZ in resected hippocampal tissue from patients with CBZ-resistant TLE (strong evidence)

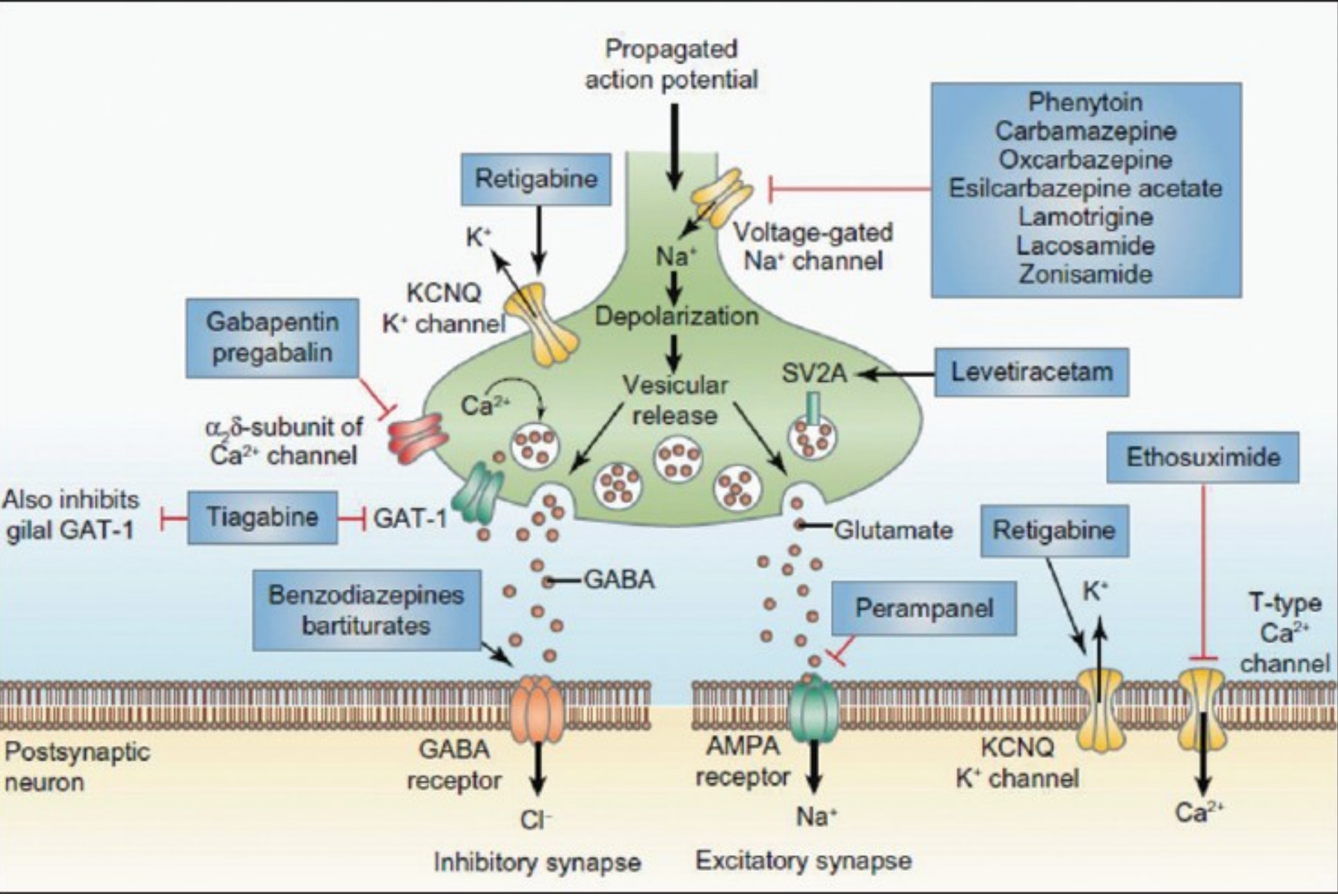
Remy et al. A novel mechanism underlying drug resistance in chronic epilepsy. Ann Neurol 2003

- Changes in $GABA_A$ receptor subtypes in brain tissue from patients with refractory TLE (benzodiazepine)

Loup et al. J Neurosci 2000

Clinical suggestion

➢ New AED to other targets



Singh. Muller J Med Sci Res 2014

Gene variant hypothesis

- Variations in genes associated with AED pharmacokinetics and pharmacodynamics cause drug resistance
- These genes include metabolic enzymes, ion channels, and certain neurotransmitter receptors that are targets for AED

Depondt. The potential of pharmacogenetics in the treatment of epilepsy. Eur J Paediatr Neurol 2006

Gene variant hypothesis

- Intronic single nucleotide polymorphism (SNP) in
- *SCN1A* → CBZ resistance
- *SCN2A* → responsiveness of various AEDs

Still inconsistent !

Abe et al. *Br J Clin Pharmacol* 2008 (Japanese)
Kwan et al. Pharmacogenet Genomics 2008 (Chinese)
Lakhan et al. *Br J Clin Pharmacol* 2009 (Indian)

- Association between *CYP2C9* polymorphism and phenytoin dose requirement (strongest evidence)

van der Weide et al. Pharmacogenetics 2001

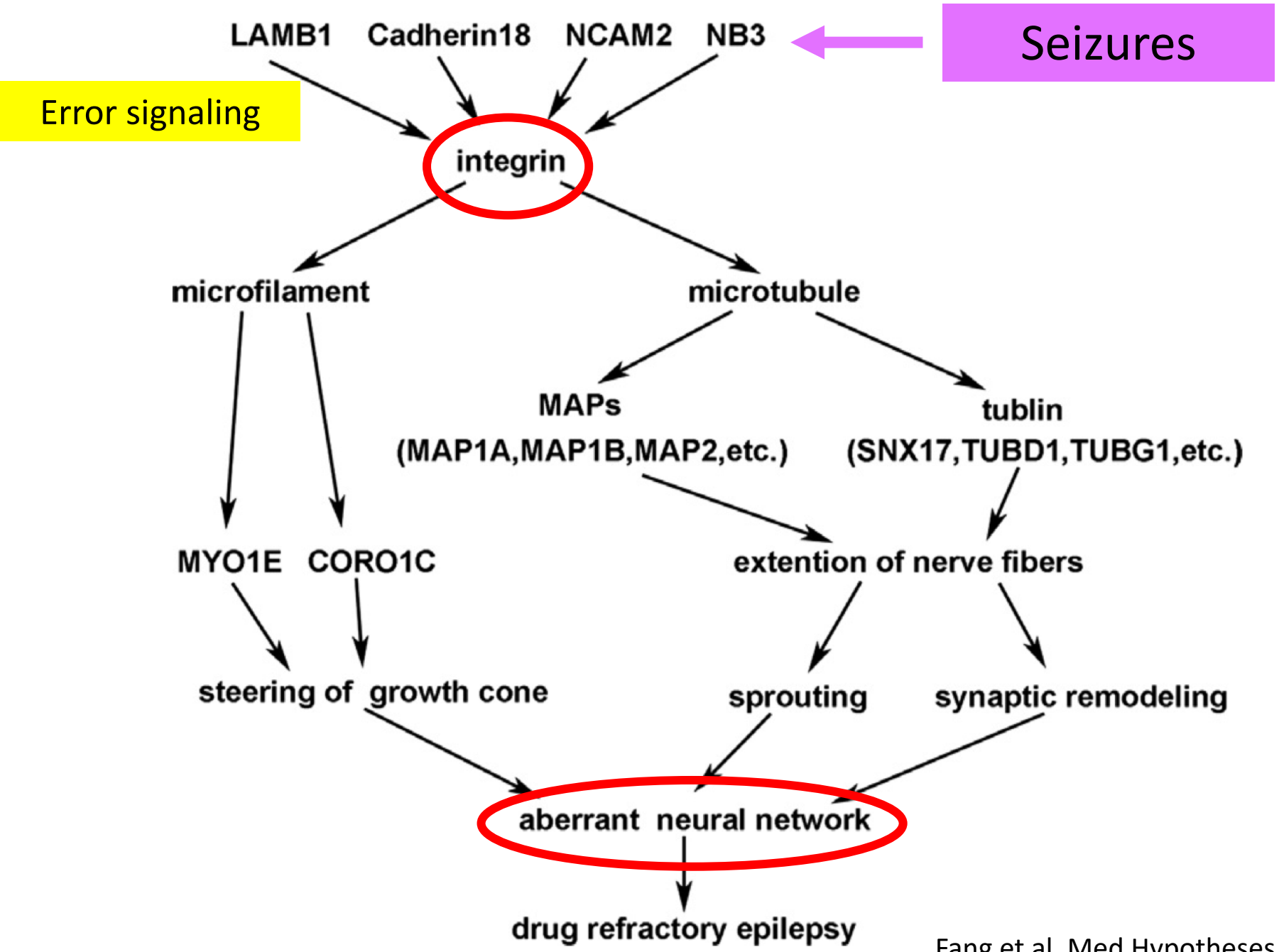
Clinical suggestion

➢ Choose of AED (future & better pharmacogenomics)

Neuronal network hypothesis

- Seizure-induced degeneration and remodeling of the neural network
- Alterations of brain plasticity including axonal sprouting, synaptic reorganization, neurogenesis and gliosis → abnormal growth of axons
- Abnormal neural network
  - Suppress the brain's seizure control system
  - Restrict AED from accessing neuronal targets

Fang et al. A new hypothesis of drug refractory epilepsy: neural network hypothesis. Med Hypotheses 2011



Fang et al. Med Hypotheses 2011

Neuronal network hypothesis

- Mainly investigated in TLE
- Can not be explained in all patients

Clinical suggestion

➢ Early treatment to prevent recurrent seizure ?

Intrinsic severity hypothesis

- Common neurobiological factors contribute to both epilepsy severity and drug resistance
- Phenotypic variation among individuals
- More severe epilepsy is more difficult to treat with AEDs
- Need to identify genetic mechanism that account for variations in severity of epilepsy

Rogawski. The intrinsic severity hypothesis of pharmacoresistance to AEDs. Epilepsia. 2013

Intrinsic severity hypothesis

- High pretreatment seizure frequency (> 10) is an important predictor for refractory epilepsy

Camfield et al. Neurology 1996

- However, starting AED treatment after the first tonic-clonic seizure did not improve the prognosis of epilepsy

Musicco et al. First Seizure Trial Group (FIRST Group). Neurology 1997

- Early treatment was associated with seizure reduction in the first 1–2 years, but rates of long-term remission were as same as deferred treatment

Marson et al. a randomized controlled trial. Lancet 2005

Intrinsic severity hypothesis

New therapeutic strategy

- Not be intended to eradicate the underlying epilepsy
- Not be intended to target brain excitability mechanisms involved in seizure generation or propagation, as do currently available AEDs
- Focus on reducing epilepsy severity

Rogawski. The intrinsic severity hypothesis of pharmacoresistance to AEDs. Epilepsia. 2013

DRE: SUMMARY

- Drug resistance is multifactorial depending on causes of epilepsy and several mechanisms
- Predictors of AED resistance is vary (individual)
- Be aware of pseudo-DRE
- No stand-alone mechanism for DRE
- Currently, transporter hypothesis is the most cited hypothesis
- Looking forward to the newer AEDs / new treatment strategy in the near future

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Thank You