ANTI-EPILEPTIC THERAPY

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Introduction

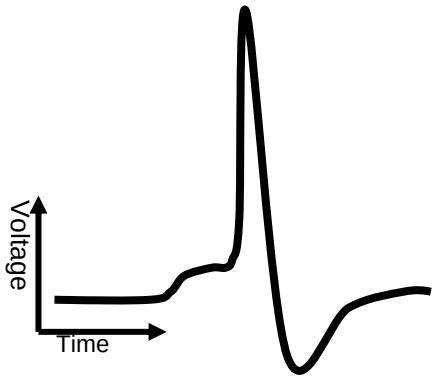
Epilepsy is a common, and commonly misunderstood, chronic medical condition. Within the first two decades of life, approximately 5% of children will have experienced some form of convulsion. A significant majority of these seizures will be acute provoked events, often in the context of a febrile illness, and not the recurrent unprovoked seizures which are the hallmark of epilepsy. Amongst all children who have a single unprovoked seizure, only about 40% of them will ever have a second (Hauser, 1993; Guerrini, 2006; Sadleir, 2007; Pohlmann-Eden, 2006). Around 20% of patients experiencing a convulsion of some type will then go on to develop epilepsy: by the age of 20 years, approximately 1% of the population has been diagnosed with this condition (Hauser, 1993). These recurrence rates vary greatly depending on such factors as what type of seizure occurred and whether there is other evidence of neurological dysfunction. For example, a patient who, at baseline, has an abnormal neurological examination, abnormal electroencephalogram, and abnormal MRI may have a risk of recurrence of approximately 90% (Lizana, 2000). Of course, this does not indicate when a subsequent seizure might occur.

Pathophysiology of Seizures

With this clinical context in mind, let's focus on the medical treatment of epilepsy and consider the various mechanisms by which anti-seizure drugs may work. We will first review the underlying pathophysiology of seizures since our medications act to interrupt these processes.

A. **The Brain's Electrical Activity**

- Excitatory neurotransmitters depolarize the cell towards 'threshold' while inhibitory transmitters hyperpolarize and prevent or delay action potentials.
- With synaptic depolarization, Na^+ channels open and the cell depolarizes further.
- This reaches a critical “tipping point” (threshold) at which point depolarization becomes self-perpetuating.
- Na^+ channels inactivate (and won’t be able to re-activate until they have been hyperpolarized – aka “depolarization block”).
- In many neurons voltage gated Ca^{2+} channels also open as the cell is depolarized allowing calcium to flow in.
- Voltage-gated K^+ channels slowly open, thereby repolarizing the neuron.
- A 'low-threshold spike’ occurs in some central neurons:
    - Hyperpolarization primes T-type Ca^{2+} channels, which then open with depolarization at relatively negative potentials.
    - Ca^{2+} enters and the cell depolarizes, giving rise to a Na^+ spike or, in some cells, a Ca^{2+} spike with a prolonged depolarization.



B. **Mechanisms of Epileptogenesis**:

Cellular: Many changes can occur at the cellular level that may promote seizures, or, to put it in a neuronal perspective, that favors excitation over inhibition (eg. altered synaptic anatomy and pharmacology, altered glial function, and abnormal synchronous bursting)

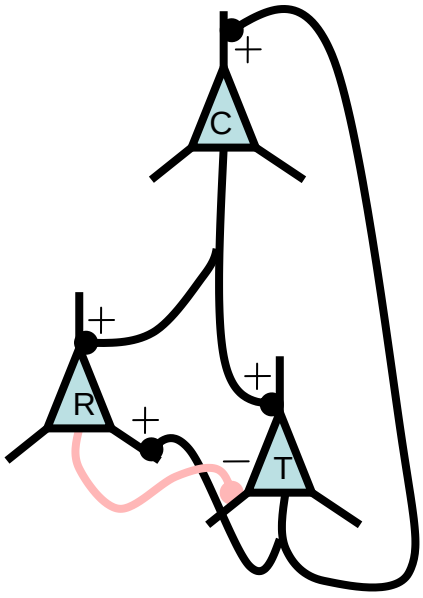
Local and Regional Networks (Focal Seizures):

- Altered synaptic anatomy, physiology & pharmacology – “pathological plasticity”
- Bursting neurons entrain other neurons in local network: hippocampus, thalamus

- Neurons within a hippocampal circuit fire together, with a frequency dependent on the recording conditions. However, an electrical stimulus delivered to one neuron within that network- but at a higher frequency (4 Hz), can entrain the entire network to fire more rapidly **within a few stimulations**! This sort of plasticity is good for memory, but detrimental if the hippocampal circuit 'learns' to participate in seizures.
- A reduction in inhibition also may produce hyperexcitability. A strong body of work on this topic uses the pilocarpine model of seizures. In this model, animals are made to have severe seizures with the chemical convulsant pilocarpine. Those that survive go into a 'latent' period, without seizures, and emerge from that having partial seizures with or without secondary generalized seizures. This model thereby reproduces many aspects of human epilepsy. In these animals, there are more $GABA_A$ receptors in the hippocampus (greater responses to GABA), suggesting an 'attempt' of the brain to increase inhibition. However, the subunit constitution of the receptors has changed. This begins in the latent period and thus may underlie the increased propensity to have seizures *(i.e.,* epileptogenesis).
- Animals can have epilepsy induced by 'kindling.' In the kindling model, a sub-convulsive electrical stimulus is delivered repeatedly. Eventually, seizures occur in response to this stimulus, and spontaneous seizures may occur. Hippocampal neurons after kindling are more sensitive to glutamate (NMDA-type receptors), due in part to reduced voltage-dependent Mg^{2+} block. These neurons show prolonged NMDA receptor (ionophore) open and burst times. Such a change could come about by a variety of mechanisms. In support of this is the finding that the NMDA blocker MK-801 can retard kindling. Interestingly, MK-801 cannot prevent seizures, showing there is a difference between *epileptogenesis* and *seizure genesis.*
- So, to summarize the pathophysiology of focal seizures: some injury, whether it be inborn or acquired (tumor, trauma, infection, etc.,) changes the physiology of synapses to favor excitation over inhibition. *Remember that seizures involve not only hyperexcitability but also hypersynchrony*. Eventually, this local network is large enough to produce a clinical seizure when it fires, the correlate being abnormal function of that part of the brain with corresponding epileptiform activity on the EEG. If this process evolves further, seizure activity may not remain local or 'focal,' but may 'generalize,' or spread throughout the brain; convulsions or generalized seizures may result.

Mechanisms of Primary (Genetic) Generalized Epilepsy: In some patients, seizures are “generalized” from the outset. This is not just an academic issue - not all medications are effective for both focal-onset and generalized-onset seizures and some can make generalized seizures worse. For example, carbamazepine, which can be very effective in focal-onset epilepsy (with or without secondary generalization), is not so effective for (and can worsen) genetic generalized epilepsy.

The basic circuit.
Thalamocortical neurons (T in the diagram below) project from the thalamus to cortical neurons (C in the diagram) and to neurons in the thalamic reticular nucleus (R). These thalamic reticular neurons are activated by glutamatergic thalamocortical (TC) or cortical neurons and fire back an inhibitory signal to the thalamocortical neuron. This quiets the next TC volley for a short time. Thus, oscillations occur- firing interrupted by quiet epochs. This occurs normally in sleep and is the basis for sleep spindles. The pharmacology of the synapses differs subtly, too, with $GABA_A$ receptors predominant in the thalamic reticular nucleus and $GABA_B$ receptors in TC neurons.



For this circuit to be highly synchronized, the transmission of signals must be precisely timed. In **childhood absence seizures**, there is intermittent highly synchronous 3-4 per second spike and wave. We assume that this circuitry is faulty, but the exact pathophysiology (there could be more than one mechanism) is uncertain.

Why doesn't hypersynchrony and seizures occur all the time?
Inhibition of nRT neurons by other nRT neurons causes neighboring TC circuits to fire at a slightly different time, i.e., there is less synchronous bursting. Individual TC neurons may still display oscillatory bursting, but the entire network will tend to be *'de-synchronized.'*

One mechanism by which seizures could occur is as follows: Decreasing inhibitory connections among nRT neurons will enhance synchronization in nearby nRT-TC circuits, allowing all the TC neurons to fire simultaneously. This synchronous activity is what occurs during a seizure.

Therapy, therefore, focuses on excitatory or inhibitory mechanisms: ion channels, receptors, and associated proteins to decrease excitation or increase inhibition.

ANTI-EPILEPTIC DRUGS AND MECHANISMS OF DRUG ACTION

Drug (Generic name)	Mechanism/ Target	Indication	Pharmacokinetics (metab, half-life (h), other)	Adverse Effects*	
				Common	Serious but rare
Carbamazepine	Na^+	**FE**	Hepatic, 8-24, autoinduction	Hyponatremia	Leucopenia, hepatitis
Clobazam	GABAR	GE (LGS)	Hepatic, 36-42, active metabolite	Somnolence	Respiratory depression
Diphenylhydantoin (Phenytoin)	Na^+	**FE**	Hepatic, 10-30, non-linear elimination	Gingival hyperplasia	Bone marrow suppression
Eslicarbazepine	Na^+	FE	Hepatic, 13-20	Hyponatremia	None yet
Ethosuximide	Ca^{2+}	**ABS**	Hepatic, 30-40	GI upset, Headache	None
Ezogabine	K^+	FE	Hepatic, 7-11	Sedation	Hallucinosis, blue pigmentation
Felbamate	Na^+, GABAR	FE & GE	Hepatic, 20-23	Anorexia, insomnia	Hepatic failure, aplastic anemia
Gabapentin	Ca^{2+}	FE	Renal, 5-7, absorbed via saturable carrier in the gut	Sedation, weight gain	None
Lacosimide	Na^+	FE	Hepatic, 13 hours	Dizziness, nausea	None
Lamotrigine	Na^+, Ca^{2+}	FE & **GE**	Hepatic, 15-30	Insomnia	Stevens Johnson Syndrome
Levetiracetam	SV2	FE	Renal, 6-8	Sleepiness, psychiatric disturbance	None
Lorazepam	GABAR	FE & GE	Hepatic, 40 (neonates), 10-12 hours (kids and adults)	Sedation	Respiratory depression
Oxcarbazepine	Na^+	**FE**	Hepatic, 8-15	Hyponatremia, ataxia, diplopia	Symptomatic hyponatremia
Perampanel	AMPAR	FE	Hepatic, 105	Sedation, imbalance	None so far
Phenobarbital	GABAR	FE & GE	Hepatic, 100	Sedation (adults); hyperactivity (kids)	Respiratory depression
Pregabalin	Ca^{2+}	FE	Renal, 5-7	Sedation, weight gain	None
Rufinamide	Na^+	LGS	Hepatic, 6-10	QT shortening, headache, somnolence	None
Topiramate	Na^+, GABAR	FE & GE	Hepatic/Renal, 20-30	Cognitive slowing, paresthesias, weight loss	Renal stones, glaucoma, oligohydrosis
Valproic acid	Na^+, Ca^{2+}	FE & **GE**	Hepatic, 10-20	Tremor, hair loss, weight gain, thrombocytopenia	Hepatitis, pancreatitis,
Vigabatrin	GABA-T	FE, IS	Renal (80% excreted unchanged), 6-8 hours	Somnolence, tremor, headache	Concentric visual field loss
Zonisamide	Na^+, Ca^{2+}, GABAR	FE & GE	Hepatic, 50-70, no effect on P450	Weight loss, paresthesias	Renal stones, glaucoma, oligohydrosis

Key: (bold and underlined **drug names** in the table above are considered first line therapy for the bolded and underlined type of epilepsy) Mechanism: K^+ = increased voltage gated potassium channel conductance, Na^+ = decreased voltage gated sodium channel conductance, Ca^{2+} = decreased voltage gated calcium channel conductance, GABAR = increase conductance of GABA-A receptor, GABA-T = inhibition of GABA transaminase, SV2 = acts on synaptic vesicle protein SV2, AMPAR = AMPA-receptor antagonist; Indication: FE= Focal Epilepsy, GE = Generalized Epilepsy, ABS = Absence only, LGS = Lennox-Gastaut Syndrome, IS = infantile spasms; Pharmacokinetics: primary metabolic pathway (hepatic or renal or both), adult half life (hours), other important fun facts if any; Adverse Effects: Most antiepileptic drugs have been associated with severe dermatologic reactions such as Stevens Johnson Syndrome. Also, so far no antiepileptic drug has been shown to be truly safe in pregnancy and most have been associated with an increased risk of fetal malformations.

Anti-seizure drugs can be difficult to use because of toxicity and drug interactions. In general, the major goals are: (1) No seizures, (2) No side effects, with (3) the least amount of medication possible.

Planning an Antiepileptic Regimen

- Take patient factors such as age, other medications, and health status (hepatic or renal disease) into account.
- Select the proper drug for the seizure type
- Consider patient's comorbidities (eg. with depression, avoid levetiracetam and consider lamotrigine)
- Determine the initial dosage based on weight and potential toxicity or interactions.
- Increase the dosage until the therapeutic effect is achieved or until limited by side effects or toxicity.
- Monitor levels as indicated (total/free; metabolites).
- Use highest tolerated dosage and add second drug if therapeusis is inadequate.
- If possible, taper the first drug off. Don't stop abruptly.

Acknowledgements

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