Classification of AEDs

Classical

- Phenytoin
- Phenobarbital
- Primidone
- Carbamazepine
- Ethosuximide
- Valproate (valproic acid)
- Trimethadione (not currently in use)

Newer

- Lamotrigine
- Felbamate
- Topiramate
- Gabapentin
- Tiagabine
- Vigabatrin
- Oxycarbazepine
- Levetiracetam
- Fosphenytoin

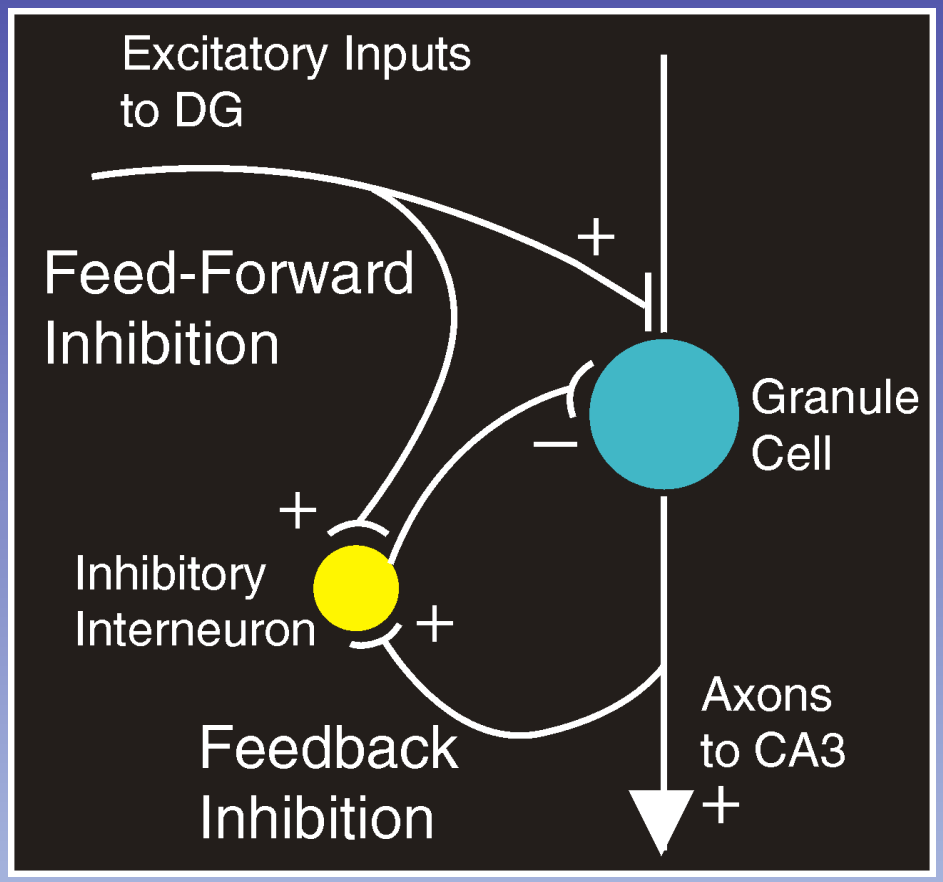
In *general*, the newer AEDs have less CNS sedating effects than the classical AEDs

Cellular Mechanisms of Seizure Generation

- **Excitation (too much)**
  - **Ionic—inward Na^+, Ca^{++} currents**
  - **Neurotransmitter—glutamate, aspartate**

- **Inhibition (too little)**
  - **Ionic—inward Cl^-, outward K^+ currents**
  - **Neurotransmitter—GABA**

Basic Mechanisms Underlying Seizures and Epilepsy



- **Feedback and feed-forward inhibition, illustrated via cartoon and schematic of simplified hippocampal circuit**

Babb TL, Brown WJ. Pathological Findings in Epilepsy. In: Engel J. Jr. Ed. Surgical Treatment of the Epilepsies. New York: Raven Press 1987: 511-540.

Neuronal (Intrinsic) Factors Modifying Neuronal Excitability

- **Ion channel type, number, and distribution**
- **Biochemical modification of receptors**
- **Activation of second-messenger systems**
- **Modulation of gene expression (e.g., for receptor proteins)**

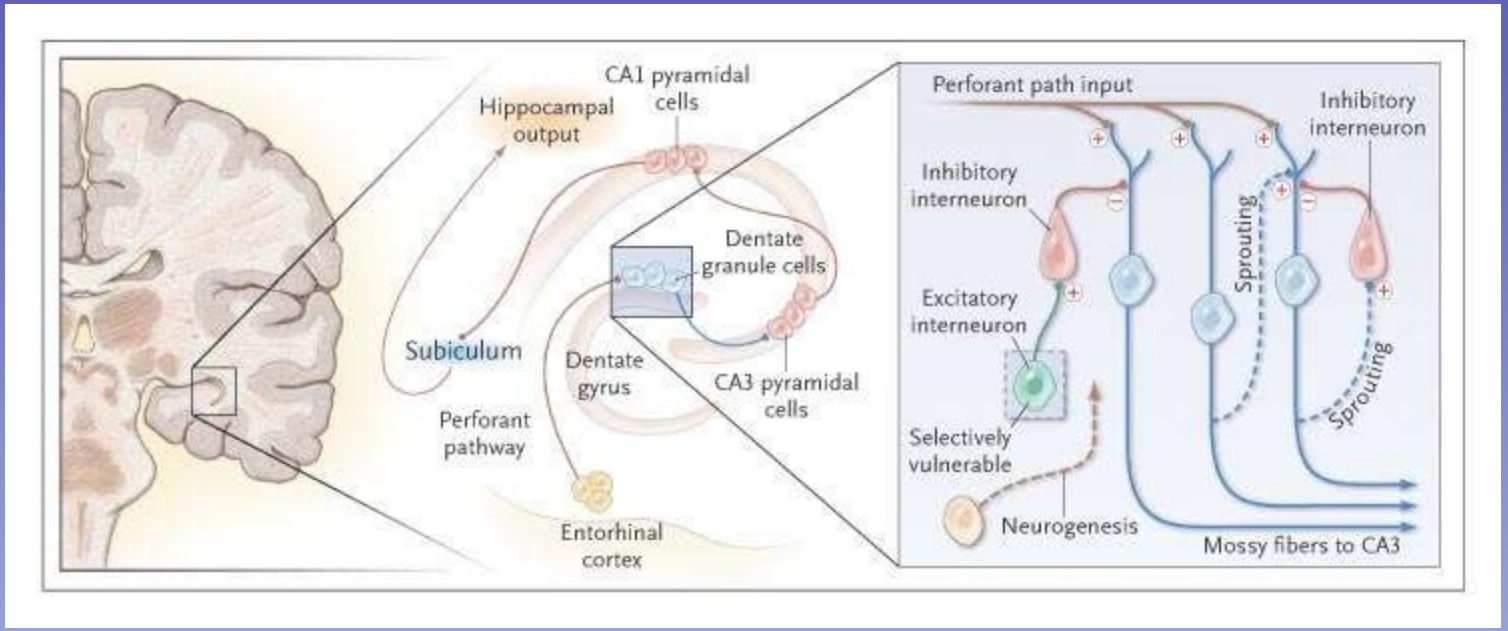
Extra-Neuronal (Extrinsic) Factors Modifying Neuronal Excitability

- **Changes in extracellular ion concentration**
- **Remodeling of synapse location or configuration by afferent input**
- **Modulation of transmitter metabolism or uptake by glial cells**

Mechanisms of Generating Hyperexcitable Networks

- **Excitatory axonal "sprouting"**
- **Loss of inhibitory neurons**
- **Loss of excitatory neurons "driving" inhibitory neurons**

Hippocampal Circuitry and Seizures



dr shabeel

Targets for AEDs

- Increase inhibitory neurotransmitter system—GABA
- Decrease excitatory neurotransmitter system—glutamate
- Block voltage-gated inward positive currents—Na^+ or Ca^{++}
- Increase outward positive current—K^+
- Many AEDs pleiotropic—act via multiple mechanisms

Epilepsy—Glutamate

- **The brain's major excitatory neurotransmitter**
- **Two groups of glutamate receptors**
  - **Ionotropic—fast synaptic transmission**
    - NMDA, AMPA, kainate
    - Gated Ca^{++} and Gated Na+ channels
  - **Metabotropic—slow synaptic transmission**
    - Quisqualate
    - Regulation of second messengers (cAMP and Inositol)
    - Modulation of synaptic activity
- **Modulation of glutamate receptors**
  - **Glycine, polyamine sites, Zinc, redox site**

Epilepsy—Glutamate

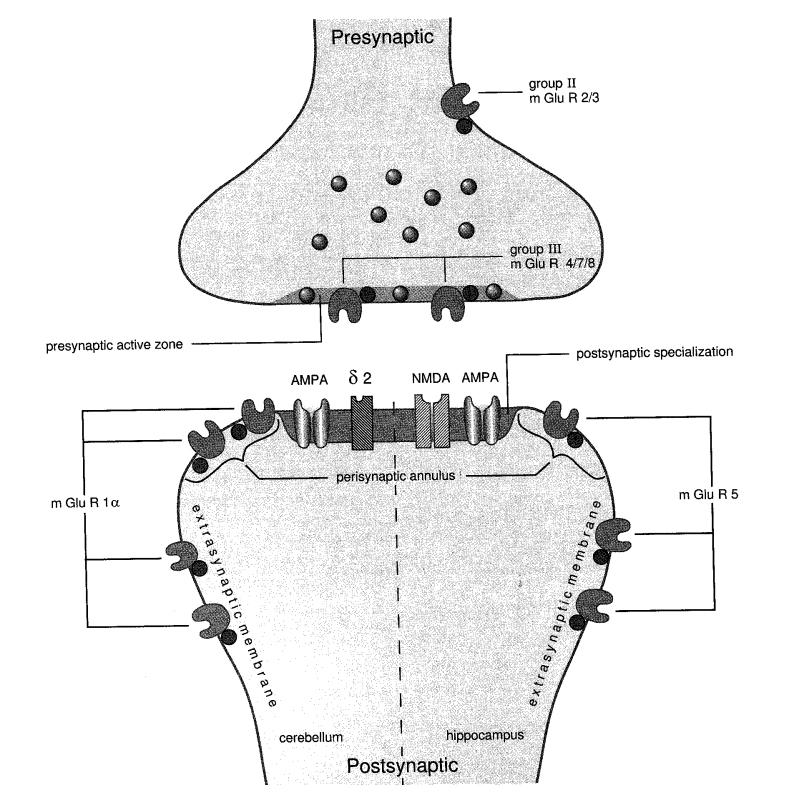


Diagram of the various glutamate receptor subtypes and locations

From Takumi et al, 1998

Glutamate Receptors as AED Targets

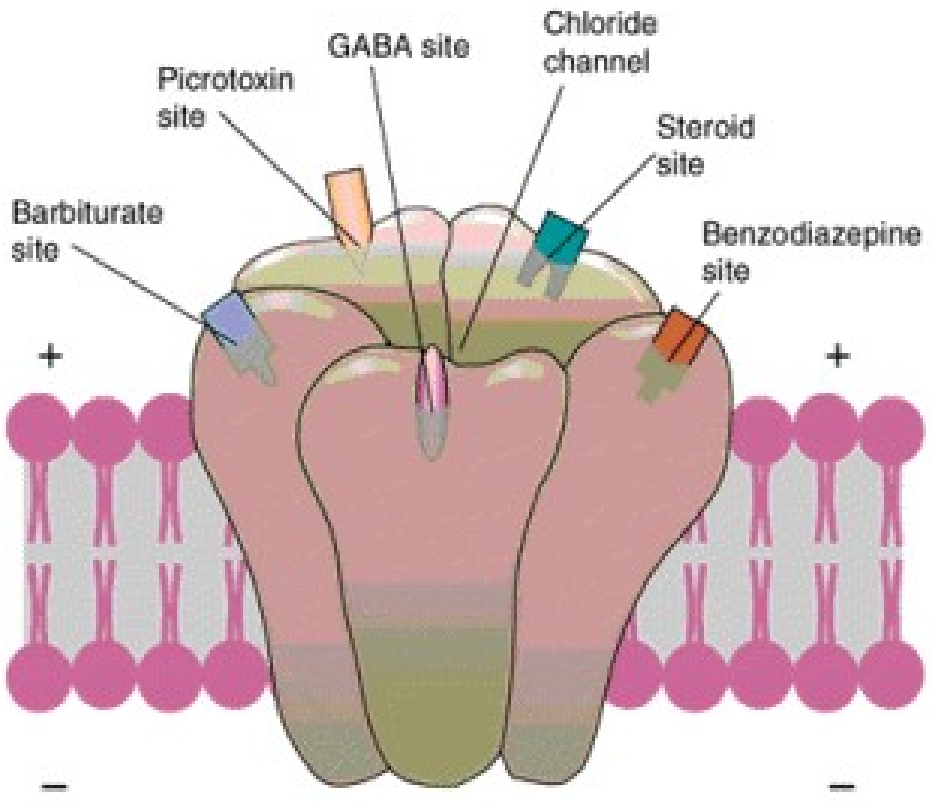
- **NMDA receptor sites as targets**
  - Ketamine, phencyclidine, dizocilpine block channel and have anticonvulsant properties but also dissociative and/or hallucinogenic properties; open channel blockers.
  - Felbamate antagonizes strychnine-insensitive glycine site on NMDA complex
- **AMPA receptor sites as targets**
  - Topiramate antagonizes AMPA site

Epilepsy—GABA

- Major inhibitory neurotransmitter in the CNS
- Two types of receptors
  - $GABA_A$—post-synaptic, specific recognition sites, linked to Cl^- channel
  - $GABA_B$ —presynaptic autoreceptors, mediated by K^+ currents

$GABA_A$ Receptor

► **Schematic Illustration of a $GABA_A$ Receptor, with Its Binding Sites**



AEDs That Act Primarily on GABA

- **Benzodiazepines (diazapam, clonazapam)**
  - **Increase frequency of GABA-mediated chloride channel openings**
- **Barbiturates (phenobarbital, primidone)**
  - **Prolong GABA-mediated chloride channel openings**
  - **Some blockade of voltage-dependent sodium channels**

AEDs That Act Primarily on GABA

Gabapentin

- **May modulate amino acid transport into brain**
- **May interfere with GABA re-uptake**

Tiagabine

- **Interferes with GABA re-uptake**

Vigabatrin (not currently available in US)

- **elevates GABA levels by irreversibly inhibiting its main catabolic enzyme, GABA-transaminase**

Na+ Channels as AED Targets

- Neurons fire at high frequencies during seizures
- Action potential generation is dependent on Na+ channels
- Use-dependent or time-dependent Na+ channel blockers reduce high frequency firing without affecting physiological firing

AEDs That Act Primarily on Na+ Channels

Phenytoin, Carbamazepine

- **Block voltage-dependent sodium channels at high firing frequencies—use dependent**

Oxcarbazepine

- **Blocks voltage-dependent sodium channels at high firing frequencies**
- **Also effects K+ channels**

Zonisamide

- **Blocks voltage-dependent sodium channels and T-type calcium channels**

Ca^{2+} Channels as Targets

- Absence seizures are caused by oscillations between thalamus and cortex that are generated in thalamus by T-type (transient) Ca^{2+} currents
- Ethosuximide is a specific blocker of T-type currents and is highly effective in treating absence seizures

What about K+ channels?

- K+ channels have important inhibitory control over neuronal firing in CNS—repolarize membrane to end action potentials
- K+ channel agonists would decrease hyperexcitability in brain
- So far, the only AED with known actions on K+ channels is valproate
- Retiagabine is a novel AED in clinical trials that acts on a specific type of voltage-dependent K+ channel

Pleiotropic AEDs

Felbamate

- Blocks voltage-dependent sodium channels at high firing frequencies
- May modulate NMDA receptor via strychnine-insensitive glycine receptor

Lamotrigine

- Blocks voltage-dependent sodium channels at high firing frequencies
- May interfere with pathologic glutamate release
- Inhibit Ca++ channels?

The Cytochrome P-450 Isozyme System

- **The enzymes most involved with drug metabolism**
- **Enzymes have broad substrate specificity, and individual drugs may be substrates for several enzymes**
- **The principle enzymes involved with AED metabolism include CYP2C9, CYP2C19, CYP3A**

Enzyme Inducers/Inhibitors: General Considerations

- **Inducers: Increase clearance and decrease steady-state concentrations of other drugs**
- **Inhibitors: Decrease clearance and increase steady-state concentrations of other drugs**

The Cytochrome P-450 Enzyme System

Inducers	**Inhibitors**
phenobarbital	valproate
primidone	topiramate (CYP2C19)
phenytoin	oxcarbazepine (CYP2C19)
carbamazepine	felbamate (CYP2C19)
felbamate (CYP3A)	(*increase phenytoin*,
topiramate (CYP3A)	*phenobarbital*)
oxcarbazepine (CYP3A)	

AEDs and Drug Interactions

- **Although many AEDs can cause pharmacokinetic interactions, several newer agents appear to be less problematic.**

- **AEDs that do not appear to be either inducers or inhibitors of the CYP system include:**
  - **Gabapentin**
  - **Lamotrigine**
  - **Tiagabine**
  - **Levetiracetam**
  - **Zonisamide**

Carbamazapine

- First line drug for partial seizures
- Inhibits Na+ channels—use dependent
- Half-life: 6-12 hours
- Adverse effects: CNS sedation. Agranulocytosis and aplastic anemia in elderly patients, rare but very serious adverse. A mild, transient leukopenia (decrease in white cell count) occurs in about 10% of patients, but usually disappears in first 4 months of treatment. Can exacerbate some generalized seizures.
- Drug interactions: Stimulates the metabolism of other drugs by inducing microsomal enzymes, stimulates its own metabolism. This may require an increase in dose of this and other drugs patient is taking.

Phenobarbital

- Partial seizures, effective in neonates
- Second-line drug in adults due to more severe CNS sedation
- Allosteric modulator of $GABA_A$ receptor (increase open time)
- Absorption: rapid
- Half-life: 53-118 hours (long)
- Adverse effects: CNS sedation but may produce excitement in some patients. Skin rashes if allergic. Tolerance and physical dependence possible.
- Interactions: severe CNS depression when combined with alcohol or benzodiazapines. Stimulates cytochrome P-450

Primidone

- Partial seizures
- Mechanims—see phenobarbital
- Absorption: Individual variability in rates. Not highly bound to plasma proteins.
- Metabolism: Converted to phenobarbital and phenylethyl malonamide, 40% excreted unchanged.
- Half-life: variable, 5-15 hours. PB ~100, PEMA 16 hours
- Adverse effects: CNS sedative
- Drug interactions: enhances CNS depressants, drug metabolism, phenytoin increases conversion to PB

Benzodiazapines (Diazapam and clonazapam)

- Status epilepticus (IV)
- Allosteric modulator of $GABA_A$ receptors—increases frequency
- Absorption: Rapid onset. Diazapam—rectal formulation for treatment of SE
- Half-life: 20-40 hours (long)
- Adverse effects: CNS sedative, tolerance, dependence. Paradoxical hyperexcitability in children
- Drug interactions: can enhance the action of other CNS depressants

Valproate (Valproic Acid)

- Partial seizures, first-line drug for generalized seizures.
- Enhances GABA transmission, blocks Na+ channels, activates K+ channels
- Absorption: 90% bound to plasma proteins
- Half-life: 6-16 hours
- Adverse effects: CNS depressant (esp. w/ phenobarbital), anorexia, nausea, vomiting, hair loss, weight gain, elevation of liver enzymes. Hepatoxicity is rare but severe, greatest risk <2 YO. May cause birth defects.
- Drug interactions: May potentiate CNS depressants, displaces phenytoin from plasma proteins, inhibits metabolism of phenobarbital, phenytoin, carbamazepine (P450 inhibitor).

Ethosuximide

- Absence seizures
- Blocks T-type Ca++ currents in thalamus
- Half-life: long—40 hours
- Adverse effects: gastric distress—pain, nausea, vomiting. Less CNS effects that other AEDs, transient fatigue, dizziness, headache
- Drug interactions: administration with valproate results in inhibition of its metabolism