Antiepileptic mechanisms of action

- Modulate voltage-dependent Na⁺, Ca²⁺, & K⁺ ion channels
- ↑GABA-mediated inhibitory neurotransmission
  - (–) Voltage-dependent Na⁺ channels: phenytoin, carbamazepine, valproic acid, lamotrigine, felbamate, topiramate, zonisamide (bind to aromatic binding sites)
  - (–) L-type Ca²⁺ channel: gabapentin
- ↓Glutamate excitatory transmission
  - (–) NMDA receptor: felbamate
  - (–) AMPA/kainate receptor: topiramate

EXCITATORY SYSTEMS

Excitatory amino acid (EAA) receptors

- Four classes, two families
  - iGluRs: Ligand-gated ion channel glutamate receptors (3 classes in this family)
    - NMDA: N-methyl-D-aspartic acid
    - AMPA: (S)-2-amino-3-propionic acid
    - KA: kainic acid
  - mGluRs: G-protein coupled metabotropic glutamate receptors (1 class in this family)
- Antagonists of these excitatory receptors are potential neuroprotective agents, cognitive enhancers, and anticonvulsants

Signal transduction

- Four methods of signal transduction
  - Enzyme linked: multiple actions
  - Ion channel linked: speedy
  - G-protein linked: amplifier
  - Nuclear/gene linked: long lasting
- Principles of signal transduction
  - Agonists have both affinity (Kₐ) and intrinsic activity (α efficacy)
    - Agonists desensitize receptors
  - Antagonists only have affinity (Kₐ)
    - Antagonists can be competitive (change affinity Kₐ) or non-competitive (change intrinsic activity α)
    - Antagonists sensitize receptors

mGluRs: metabotropic glutamic acid receptors

- mGluR₁ & mGluR₅ antagonists: neuroprotective for traumatic brain injury
- mGluR₂ positive allosteric modulators & mGluR₅ negative allosteric modulators: anxiolytics
- mGluR₄ positive allosteric modulators: Parkinson’s disease treatment

NMDA receptor complex

- Both ligand gated and voltage dependent
- Transmitter recognition site: NMDA agonists or competitive antagonists bind here
- Positive modulator sites: glycine & polyamines bind to these
- Other sites: redox modulator site, zinc binding site, ion channel binding site
- Positive allosteric modulator: when bound, keeps or converts receptor to active form
INHIBITORY SYSTEMS

GABAergic systems: sites of AED drug action

- (+) L-glutamic acid decarboxylase (GAD) → ↑biosynthesis of GABA from glutamate
  - Gabapentin, valproic acid
  - Requires cofactor Vit B₆
- (+) mGluRs → ↑release of GABA (??)
- (+) Post-synaptic GABAₐₙ/BZD receptors → ↑Cl⁻ influx → hyperpolarization of neuron (inhibitory)
  - Benzodiazepines, barbiturates, neurosteroids
    - Also have anxiolytic and hypnotic-sedative action
  - Two groups of GABA receptors: Cl⁻ channel coupled and G-protein coupled
    - Cl⁻ channel coupled: GABAₐ, GABAₐₖ
    - G-protein coupled: GABAₗ
- (-) GABA transporter → (-)GABA reuptake → ↑GABA available in synapse
  - Tiagabine
- (-) GABA transaminase (GABA-T) irreversibly → ↑GABA available in synapse
  - Vigabatrin
  - Requires cofactor Vit B₆

GABA and glutamate share a similar precursor

- GABA biosynthesis: glutamine → glutamate → GABA
- Fates of GABA:
  - SSADH → Krebs cycle
  - GABA → glutamate
  - Valproic acid can inhibit both of these
    - Valproic acid: inhibits end-product → negative feedback → inhibits GABA-T
    - Allylglycine: inhibits GAD → ↓GABA → ↑excitability & seizures
- GABA and glutamate have a shared precursor: glutamine (Gln)
- Biosynthesis of glutamate: L-leu + α-ketoglutaric acid → L-Glu
  - L-glutamic acid → GABA

Vitamin B₆

- Essential cofactor for both GAD (decarboxylase) & GABA-T (transaminase)
- Activates these enzymes’ substrates
- Serves as electron sink

GABA-T

- Responsible for eliminating GABA
  - Catalyzes a reversible transamination: GABA + α-ketoglutaric acid → SSA + L-glutamic acid
    - Product: succinic semialdehyde (SSA) → succinic acid → TCA cycle
    - TCA cycle metabolites: succinic acid, α-ketoglutaric acid
  - Requires cofactor: Vit B₆ (pyridoxal phosphate)
- Two types: reversible and irreversible
  - Reversible: competitive inhibition, easily overcome
  - Irreversible: more efficacious outcome
    - Gabaculine: covalently binds to Vit B₆
    - Vigabatrine: covalently binds to both GABA-T and Vit B₆