PCOL3022

Neuropharmacology

S2 2020

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Lecture 18 – Anticonvulsants

L01: Define epilepsy.

- A disorder of the brain characterised by an enduring predisposition to generate epileptic seizures
- Only need the occurrence of one unprovoked seizure to be diagnosed (don't want to wait till you have a second one before they treat you!)
- Reasons for seizure: head trauma, high fever (especially in children), alcohol withdrawal, dehydration

L02: Describe the different types of seizures.

- Focal (partial) seizure
  - Activation of neurons in a relatively small, discrete region
  - Clinical manifestation reflects region of brain where they occur (can be sensory or motor defects)
  - Complex partial seizures (temporal lobe epilepsy): impairment of consciousness (symptoms – familiarity, strangeness, automatisms (physical tics), hallucinations)
- Generalised seizure
  - Characterised by involvement of both hemispheres and widespread neuronal activation
  - Can have progression from focal to generalised seizures
  - Stages:
    1. Tonic: extension of the extremities (rigid stretching)
    2. Atonic: sudden loss of muscle tone (hence falling over)
    3. Clonic (myoclonic): repetitive muscle twitching
    4. Tonic-clonic (grand mal): distinct tonic phase followed by a clonic phase (full body spasms with intermittent relaxation)
    5. Generalised absence seizures (petit mal): brief lapse of consciousness (can look quite mild but can be a big problem, especially if driving)

L03: Describe the mechanism of action of antiepileptic drugs.

- Need balance of excitation and inhibition
  - Too much excitation leads to convulsions, anxiety, high BP, insomnia → increased levels of glutamate and decreased levels of GABA
  - Too much inhibition leads to sleep, sedation, depression, coma, low BP → increased levels of GABA and decreased levels of glutamate
- Anticonvulsants
  - 25-40% of newly diagnosed epilepsy patients are drug resistant (to at least two anticonvulsant drugs)
  - Huge variability in disease management
    - Compliance: disease for life
    - Monitor plasma levels: use this to monitor patient's compliance to treatment
  - Toxicity issues long term

- Mechanisms of anticonvulsants (green is about ↓ excitation; red is about ↑ inhibition)
  1. Enhance Na^+ channel inactivation – reduce firing frequency of neurons

     PHENYTOIN
     - Na^+ channel blockers
     - Na^+ channels are critical for initiation and propagation of APs
     - Enhance voltage gated Na^+ channel inactivation by reducing sustained high frequency firing of APs – therefore making it harder to open and thus reducing excitability
     - Well tolerated (<u>side effects</u>: dizziness, nausea, headache)
  2. Inhibit excitatory amino acid release – block Ca^{2+} channels

     KEPPRA
     - Binds to neuronal synaptic vesicle glycoprotein 2A protein (typically used to release glutamate)
     - Reduces neuronal excitability and glutamate release, thus reducing excitability

     ZARONTIN
     - Treats generalised absence seizures (lapse of consciousness)
     - T-type Ca^{2+} channel blocker
     - Well tolerated (<u>side effects</u>: nausea, diarrhoea)
  3. Block excitatory amino acid action

     FYCOMPA
     - Selective, non-competitive AMPA receptor antagonist
     - Prevents ability of glutamate to bind to AMPA receptors on post-synaptic membrane
     - Potent
  4. Enhance GABA action

     BARBITURATES
     - Can act alone or enhance actions of GABA
     - Acts on all $GABA_A$ receptors to prolong the 'open' time of the channel
     - Not used as first-class drug anymore due to unwanted sedative effects
     - <u>Side effects</u>: tiredness, anaemia, confusion

     BENZODIAZEPINES
     - Enhances the actions of GABA
     - Increases the frequency of channel opening to increase inhibition
     - Patients develop rapid tolerance
     - <u>Side effects</u>: sleepiness, poor coordination
  5. Inhibit GABA breakdown

     VIGABATRIN
     - Prevents breakdown of GABA
     - Specific inhibitor of GABA transaminase (breaks down GABA)
     - Side effects: fatigue, dizziness, loss of peripheral vision (need to monitor this constantly)
  6. Inhibit GABA uptake

     TIAGABINE
     - GAT1 inhibitor
     - Increases extracellular GABA levels
     - Well tolerated (<u>side effects</u>: sleepiness, tremor, anxiety)

- Other commonly used drugs with unknown mechanisms
  - Epilum
    - May use mechanisms 1, 2 and 5?
    - A use-dependent Na^+ channel blocker and a Ca^{2+} channel blocker (therefore decreases excitation)
    - Increases the levels of GABA (therefore increases inhibition)
    - Well tolerated (side effects: dizziness, weight gain, cannot OD as no nitrogen)
  - Topomax
    - May use mechanisms 1, 3 and 4?
    - Inhibits voltage-dependent Na^+ channels (therefore decreases excitation)
    - Antagonist at AMP receptors (therefore increases inhibition)
    - Moderately tolerated (side effects: dizziness, word retrieval problems, confusion)
  - Felbatol
    - May use mechanisms 1, 3 and 4?
    - Inhibits voltage-dependent Na^+ channels (therefore decreases excitation)
    - Antagonist at NMDA receptors
    - Positively modulates $GABA_A$ receptors (therefore increases inhibition)
    - Well tolerated (side effects: headache, weight loss, insomnia)
  - Gabapentin
    - Increases total GABA concentrations in CSF
    - Associated with decrease in NT release (mechanism 2)
    - Well tolerated (side effects: sleepiness, weight gain)

L04: Describe the genetics of epilepsy and the functional effect of a mutation that causes epilepsy.

- Brain is predisposed to seizure activity because neurons are so extensively interconnected – fine balance
- 25 genes have been found that are responsible for epilepsy
- All mutations known to cause epilepsy are found in ion channel subunits
- $GABA_A$ receptor mutation
  - Mutation in γ2 subunit $GABA_A$ receptor
  - Decrease in $GABA_A$ receptor amplitude
- Sodium channel mutation
  - Mutation in $Na_v1.1$ channel which renders it non-functional (due to protein folding errors)
  - Why does Na^+ channel loss of function mutation cause epilepsy when most common drugs for epilepsy inhibit Na^+ channels?
    - Na^+ channels are found in GABAtinergic neurons so not the kind of Na^+ channels found in presynaptic excitatory system