Central Neurotransmission

by the end of this lecture you should be able to

- predict the consequences of giving drugs which interact with CNS neurotransmission

8yr old farm Collie

- dosed with pour-on ivermectin 2 d ago
- ataxia
- blind
- tremors
- hypersalivation (may have vomited)
- generally depressed

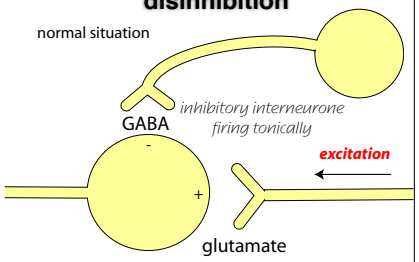
definitions

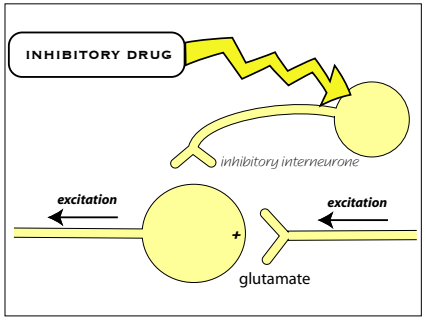
- neurotransmitter
  - acts rapidly, briefly & at short range
- neuromodulator
  - act more slowly and further away
  - responsible for most synaptic plasticity
  - not always from neurones

effects

- behavioural - ? - cellular
- depend on
  - wiring (NGF etc)
  - receptor subtypes , distribution & numbers
  - transduction mechanisms
  - neuromodulators
  - their transduction mechanisms
  - all these can change!

disinhibition





time course

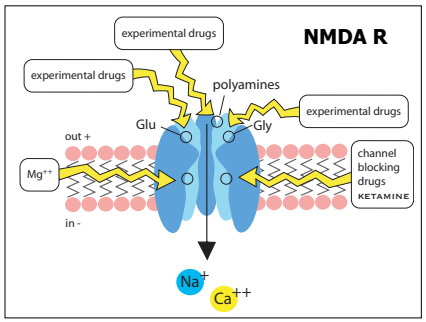
- milliseconds
  - fast transmitters
- tens of ms
  - NMDA receptors
- seconds - minutes
  - neuromodulators
- minutes - days
  - receptor up / down regulation
- days - weeks (-never)
  - neurone reconnections

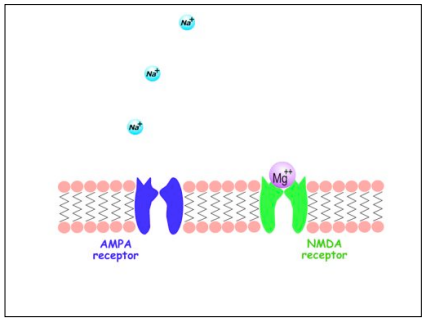
neurotransmitters

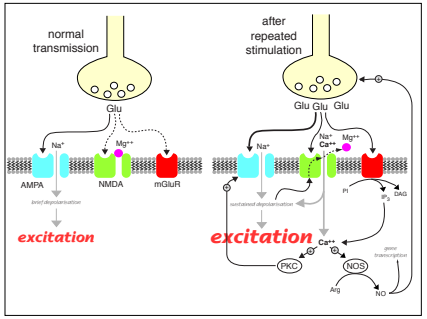
- excitatory
  - glutamate
- inhibitory
  - GABA
  - glycine
  - catecholamines
- both / either
  - 5HT
  - adenosine / ATP

glutamate receptors

- AMPA fast
  - normal transmission
- NMDA medium
  - wind up
  - pain
  - memory
- metabotropic slow (15 subtypes)
  - modulation?
- kainate fast
  - ?







glutamate

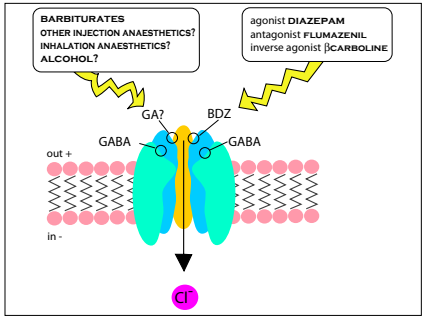
- energy metabolism
- excitotoxicity

neurotransmitters

- excitatory
  - glutamate
- inhibitory
  - GABA
  - glycine
  - catecholamines
- both / either
  - 5HT
  - adenosine / ATP

GABA / glycine receptors

- $GABA_A$
- glycine
  - postsynaptic chloride channels
- $GABA_B$
  - presynaptic, G protein coupled
- glycine / NMDA
  - on NMDA receptor
- glutamate (nematodes)

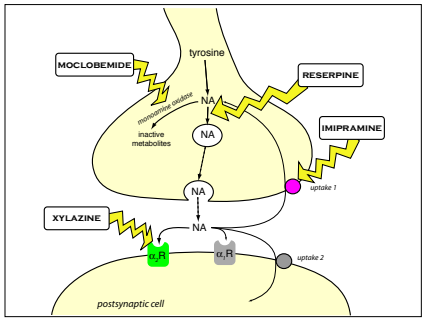


GABA / glycine receptors

- $GABA_A$
- glycine
  - postsynaptic chloride channels
- $GABA_B$
  - presynaptic, G protein coupled
- glycine / NMDA
  - on NMDA receptor
- glutamate (nematodes)

monoamine receptors

- noradrenaline
- dopamine
- 5HT
- octopamine



noradrenaline

- mostly postsynaptic α2
- mostly inhibitory
- alertness, pain, blood pressure

imidazolines

- I1
  - blood pressure
- I2
  - depression?? MAO
- I3
  - insulin release

dopamine

- currently 5 receptors
- D2
  - reward pathway
  - pituitary hormone release
  - nigrostriatal pathway
  - vomiting

5HT receptors in brain

- $5HT_{1A}$ - mood / emotion, pain?
- $5HT_{1C}$ - CSF secretion, motor function
- $5HT_{1D}$ - motor function
- $5HT_{2}$ - stereotypy, mood / emotion, hallucinations
- $5HT_{3}$ - anxiety, emesis, pain?
- + 9 other subtypes!

reuptake inhibitors

- human antidepressants
- used to alter animal behaviour

other fast transmitters

- acetylcholine
  - nAChR, mAChR
- histamine
  - H1, H2, H3
- adenosine, ATP, AMP

purinergic receptors

- adenosine
  - A1 and A2 R - G protein coupled
  - presynaptic inhibition
- ATP
  - P2x (ionotropic) P2y (metabotropic)
  - co-transmission in periphery, nociception

neuromodulators

- excitatory
  - substance P
  - neurokinins A & B
  - cholecystokinin
  - nitric oxide, carbon monoxide
  - arachidonic acid / prostaglandins
  - etc, etc

neuromodulators

- inhibitory
  - encephalins, morphine - μ, δ R
  - some dynorphins - κ R
  - cannabinoids - CB1, CB2 R
  - magnesium?
  - zinc??

adaptive processes

- cfos, cjun
- growth factors

8yr old farm Collie

- dosed with pour-on ivermectin 2 d ago
- ataxia
- blind
- tremors
- hypersalivation (may have vomited)
- generally depressed

central neurotransmitters

- glutamate is the main excitatory transmitter
- glutamate acts at AMPA (fast), NMDA (medium) and mGlu (slow)
- GABA is the main inhibitory transmitter, acting at $GABA_A$ receptors
- neuromodulators act slowly to amplify or reduce transmission
- noradrenaline, acting a α_2 receptors, causes CNS depression