Neurochem

Fri. Mar. 2/07

- most important type of transporter is the 1° transporter (Na^+/K^+ ATPase).

- 2° transporters - require an established gradient
  - ↳ same direction - symporter
  - ↳ opposite " - antitransporter.

- coca cola - made of coca plant + Kola Nut.
  - ↳ give taste + flavour.
  - ↳ provide caffeine

- before 1903, cocaine was in coca cola.
  - ↳ affects monoamine neurotransmitter in the brain.

- monoamine NT - only have one amine group.
  - ↳ dopamine, norepi, serotonin.
  - ↳ dopamine is a precursor of norepi

- most are G-protein coupled receptors.
- substantia nigra + ventral tegmentum ⇒ where dopamine is.
  + limbic system ⇒ controls mood
- dopamine is important for behaviour reinforcement, motor control.
- norepinephrine controls the sleep-wake cycle
- NT's are uptaken by transporters* } to get rid of NT. or are degraded

* present on presynaptic terminals on plasma membrane.

transporters of monoamine NT:
- DAT ⇒ let 2 Na^+ more, 1 Cl^- and 1 dopamine
  - ↳ these share molecular structure.
- one polypeptide chain but 12 transmembrane domains

- once they are in cytosol, they can either [ ] back in vesicle or be degraded.

- V_0V_1-type proton pump ⇒ pump protons into vesicle.
- Vesicular monoamine transporter (VMAT) ⇒ not very selective.
- require DAT to allow NT reuptake
- also need monoamine transporter to [ ] back in vesicle.
- DA autoreceptors - will ↓ the release of NT's.
  ↳ ⊖ve feedback system.
- cocaine blocks the uptake of NT's (blocks DAT).

Psychostimulants

- cocaine, amphetamine, methamphetamine.
- blocks transporters for dopamine ∴ have more dopamine in synaptic cleft.

amphetamine - gets into terminal by transporter or diffusion
  ↳ goes into synaptic vesicles + affects H^+ gradient.
    ∴ dopamine gets released into synaptic terminal.
  ↳ also affects MAO - degraded dopamine
    ↳ monoamine oxidase.

- ↑ arousal, alertness, give feeling of euphoria
- used to be used to treat narcolepsy (sleep-too much)
- ritilin ⇒ used to treat ADD
  ↳ is an amphetamine analog.
- also ↓'s appetite.
- creates a dependence + addictive + may cause depression.
- now still use amphetamine to treat soldiers ⇒ help them stay awake

Prozak - an inhibitor for serotonin transporter
  ↳ used to treat depression.

SSRI's - selective serotonin reuptake inhibitors
↳ ∴ ↑ amount of serotonin in the synaptic cleft.
↳ billion $ industry!

- take a month to see the effect of the drug.
- still don't have a cure for this type of mood disorder.
- by removing the transporter, you can detect an ↑ in the amount of NT (↑ lifetime) but ↓ release. ↳ ↑ synthesis.

- monoamine NT's play a role in mood + depression.
- SSRI has been used to treat depression.

Parkinson's disease - 0.2% of people over 65.
↳ some people lose the ability to move their muscles.
↳ have some tremors + @ the end cause muscle rigidity

- occurs in substantia nigra → region of the brain that is pigmented.
↳ in Parkinson's, get loss of the majority of these neurons → make dopamine.

MPTP → a toxin that kills dopaminergic neurons.
↳ in mid 1970's, early 80's, there was a shortage of heroin ∴ people tried to make an analog of heroin → meperidine (MPPP)
- Barry Kidston → tried to make MPPP. himself in his basement
↳ chemistry student.
↳ @ one point, got into problem in synthesis
↳ when he injected it into his body, he developed Parkinson's. → this is b/c he injected MPTP instead which kills dopaminergic neurons.

Hilroy

↳ ∴ affects dopaminergic neurons

MPTP - can pass through dopamine transporter
↳ neurotoxic b/c it produces free radicals in mitochondria + affect ATP production.

- if you inject MPTP into animals ⊖ DAT knockout, will not have an effect.

- ↑ # of people in China develop parkinson's → maybe b/c there is more pollution (more neurotoxins).

Neuropathic pain - caused by damages of nerve fibers ↳ require for sending signal to the brain
↳ the threhold for pain ↓'s.
↳ very hard to treat b/c still need these fibers.
↳ related to pathway that ends in thalamus + cingular cortex
- pain pathways go from the spinal cord → brain
↳ if inhibitory signal, will inhibit this pathway (mediated by GABA → K^+/Cl^- transporter) ∴ KCC2
- if you open a Cl^- channel, Cl^- will flow inside cell + act inhibitory
- in neopathic pain conditions, microglial cells will secrete BDNF + activate receptors → ↓ exp^n of KCC2 + activate NKCC1 → will cause Cl^- to accumulate inside + ∴ can exit + affect other cells