Lecture 1

Monday, 29 February 2016
11:57 AM

In vivo experiment
- Observing the effect of a beta blocker
- Determining heart rate

Ways of classifying drugs
- Therapeutic use - e.g. antihypertensive
- Mode of action (drug target) - e.g. antihistamines are histamine receptor antagonists
- Molecular structure - e.g. benzodiazepines

Drug Nomenclature
- Chemical
- Non-proprietary - pharmacologists use this
- Proprietary

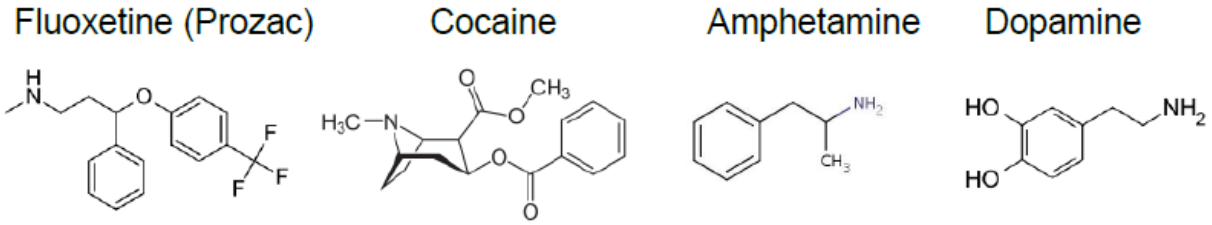
Lecture 2

Thursday, 3 March 2016
10:04 AM

<u>Drug Targets</u>
- Most drug targets are proteins
    - Transporters - control what goes in and out of the cell
    - Membrane receptors - usually transmembrane proteins which activate enzymes within the cell
    - Ion channels - on the cell membrane - CNS signalling
    - Protein synthesis - target for a variety of antibiotics
    - Enzyme inhibition
    - Regulation of gene expression - intracellular and intranuclear
- Drugs which act on the surface are small and hydrophilic
- Drugs that need to cross membrane need to be lipophilic - permeate lipid membrane
- Some drugs need to cross the blood brain barrier to act on the CNS - lipophilic
- Many drugs are designed to mimic an endogenous compound - e.g. cocaine mimics dopamine

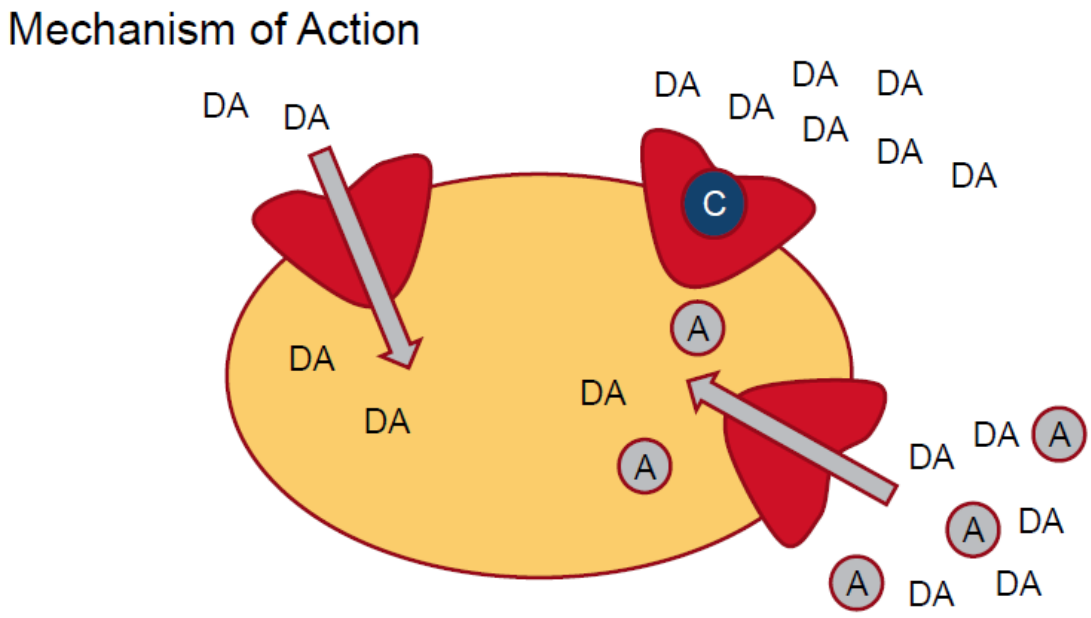
Receptors
- These are the sensing elements in the system of chemical communications that coordinates the function of all the different cells in the body.
    - Hormones
    - NTs
    - Other mediators

Transporters
- Some molecules are too hydrophilic to permeate cell membrane
- Permeating compounds like ions, NTs etc., are often too polar and hence too lipophobic to penetrate the cell walls which are made from lipids - transporters allow them to pass through

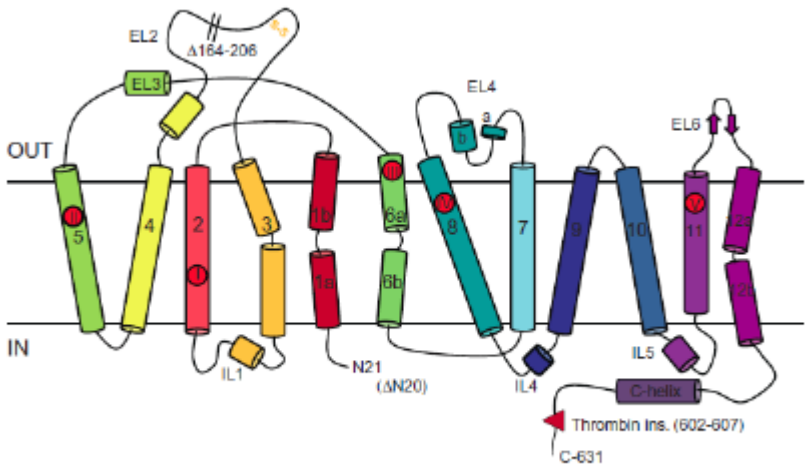
- Transporters are membrane proteins that regulate the concentration of neurotransmitters in the CNS
- e.g. dopamine will bind to a transporter and change its shape
- Antidepressants block serotonin, dopamine and noradrenaline transporters
- Cocaine - binds and blocks dopamine and serotonin transporters - antagonist which blocks re-uptake and results in build-up of NTs in the brain
- Amphetamine - act on dopamine and noradrenaline transporters - acts as a false substrate rather than an inhibitor - it is an agonist
- 

    - Amphetamine is a substrate for the transporter because they look similar to dopamine while cocaine binds to the transporter but then block it up and stop it from functioning because it is bigger

Cocaine and Amphetamine

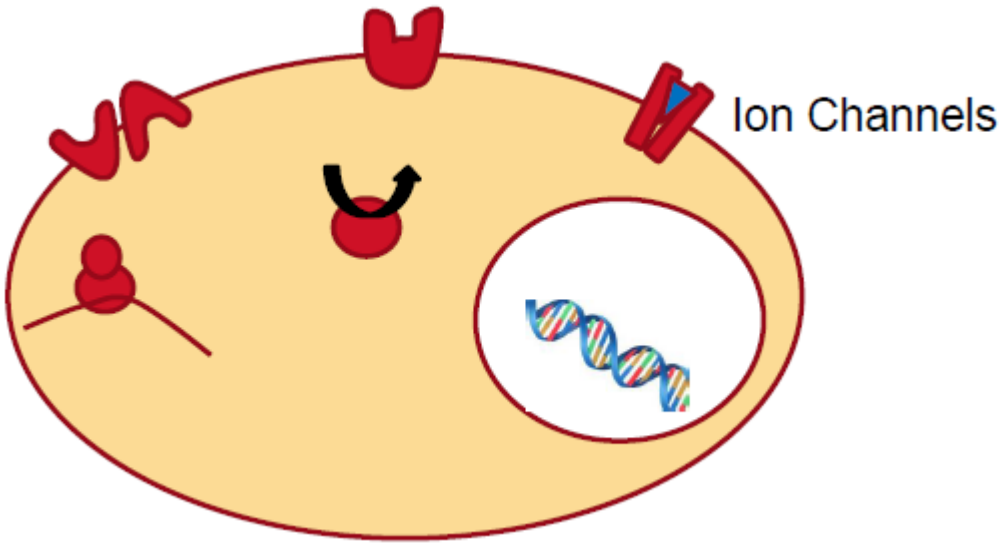
- Stimulant isolated from leaves of coca plant
- Appetite suppressant
- Topical anaesthetic (local)
- Dopamine transport inhibitor
- Na+ channel blocker - anaesthetic effects
- 

    - Catechol group (two OH groups) is essential to bind to the receptor but not the transporter
    - Cocaine is a lot bigger than dopamine so it binds but it clogs it up and prevents any dopamine from entering the cell so that the synapse becomes flooded with dopamine - antagonist action preventing reuptake
    - Amphetamine actually enters the cell so it acts as a substrate
- Structure of the dopamine transporter

- 

    - Transmembrane components - 12 domains
    - EL3 is a hydrophilic component which interacts with the cytoplasm or the outside of the cell
    - 3, 1 and 6 - fragments in the alpha helices to allow movement - important to achieve the function of binding to dopamine, changing its confirmation and then dumping it inside
    - Extracellular fragments 8-11 allow entrance pathway for dopamine into the cell
    - All these transporters use a sodium gradient to drive the transport process - when a large amount of dopamine is released into the synapse there is a change in concentration relative to the inside - to drive the dopamine back into the cell it is coupled to the sodium gradient because the concentration of sodium is higher on the outside - the sodium drags the dopamine-transporter complex into the cell - sodium dependent dopamine transporter
    - Nortriptyline prevents movement of subunit 1b - binds to the same site as dopamine because it is similar to it - extra chemical group stop 1b and 6a from moving - blocks it in an outward facing state.

Ion channels

- 

- Na+ channel sits on cell surface - normal function is to respond to electrical impulse - opens and allows sodium ions into cells and propagates the action potential to continue the signal

- Ligand-gated channels are actually receptors as they require an agonist to bind to them in order to open - metabotropic - linked to G-proteins
- Voltage-gated channels are influenced by transmembrane potential - ionotropic
- Cocaine could be used as anaesthetic for eye surgery - local anaesthetic - Sigmund Freud
- Search for similar compounds that are less addictive began - derivatives of cocaine with only the anaesthetic effects on no CNS effect
- Types of drug interaction with ion channels:
    - Orthosteric binding - drugs bind to the channel protein itself - ligand-gated channels
    - Allosteric binding - drugs binding away from the binding site and change the conformation of the channel thus blocking ions from entering
        - Benzodiazepines bind to a site distinct on $GABA_A$ receptor-ion channel complex and thus facilitate opening of the channel by inhibitory NT GABA - acts as an anaesthetic but binds allosterically to a ligand-gated channel
    - Indirect action - involves G proteins and other intermediaries
    - Altering level of expression of ion channels on cell surface
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