Pharmacology notes

Lecture 1: Welcome

History

- Hippocrates (5th century): idea of do no harm (risk vs reward)
- Paracelsus (16th century): all things (drugs) are poison and nothing is without poison: the dose permits something not to be poisonous (dose determines effect)
- Erlich (20th century): substances do not bind unless bound

Pharmacodynamics

- Way drugs interact in the body/ what the body does to the drug (target)
- Drug must be: at an effective concentration, able to bind have an effect and be selective

Pharmacokinetics

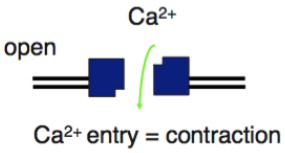
- What the drug does in the body
- Get there: drug must be absorbed, distributed and reach an effective conc
- Get out of there: drug is metabolised (usually liver) and excreted (urine/faeces)

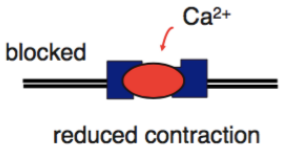
Lecture 2: drug targets

A drug will not work unless its bound

Common drug targets

1. Ion channels
   - Allow passage of ions into cell
   - Sit in the cell membrane ad control the influx of ions
   - Drugs block or modulate channel opening



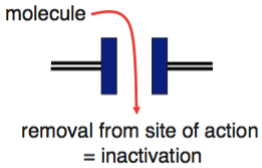


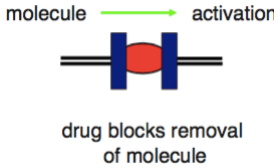
e.g. nifedipine blocks Ca channels

⇒ Reduced blood vessel constriction (relaxation)

⇒ Reduced blood pressure

2. Carrier molecules
   - Transport of molecules across lipid membranes
   - Drugs block or utalise carriers





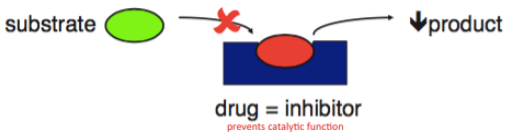
e.g. fluoxetine

⇒ Blocks serotonin uptake into nerve cells

⇒ Prolongs serotonin action (used for depression)

⇒ Uses carrier molecule to get back into the nerve terminal (more to bind)

3. Enzymes
   - Catalyse synthesis/breakdown of molecules
   - Drugs may inhibit enzymes



e.g. aspirin

⇒ Inhibits cyclo-oxygenase (COX)

⇒ Reduced synthesis of mediators of pain/fever/inflammation

   - Drugs may use enzymes

e.g. L-dopa

⇒ Uses dopa decarboxylase

⇒ Increased synthesis of dopamine

⇒ Used for parkinson's disease (increase in level of dopamine)

4. Cells receptors
   - A receptor is a biological macromolecule or complex that binds another molecule and initiates or modulates signalling or effector (ion channel or enzyme) activity within a cell
   - Located in plasma membrane or cell cytoplasm (has to be lipid soluble to get in)
   - Ligands (neurotransmitter, hormone, pharmaceutical drug or toxin) bind to binding sites (doesn't have to have an effect)
   - A ligand that binds to a receptor and activates it is called an agonist (produces an effect), mimic activity of nerve activation (and exogenous NA or Ach)

e.g. morphine (agonist) activates opioid receptors used for pain

   - A ligand that binds to a receptor without activating it will act as an antagonist (no effect produced), block nerve-evoked responses, block responses to exogenous Ach or NA

e.g. Naloxone (antagonist) blocks opioid receptors used for heroin overdose

   - Recognition sites for molecules (selectivity: a certain drug if selective for a certain receptor)
   - Muscarinic receptors are activated by muscarine
   - Nicotinic receptors are activated by nicotine

Receptor nomenclature

   - Receptors are named for cognate hormone or neurotransmitter
   - Muscarinic and nicotinic receptors are acetylcholine (Ach) receptors (separate classes of Ach receptors)
   - Adrenoceptors are activated by adrenaline and noradrenaline
   - Angiotensin receptors are activated by angiotensin
   - Alpha-adrenoceptors and beta-adrenoceptors are separate classes of adrenoceptors

	α1	α2	β1	β2
Distribution	Most common, sympathetic targeted tissue e.g. blood vessel and smooth muscle	Gut and pancreas	Heart (increase HR and contractility)	Smooth muscle of bronchioles, blood vessels of heart, liver and skeletal muscle
Respond to	Noradrenalin	Noradrenalin	Noradrenalin and adrenalin	Adrenalin
Overall effect	Stimulation (constriction)	Inhibition	Stimulation	Inhibition

Metabotropic: agonist binding triggers a series of intracellular events that produce 'second messengers' to indirectly produce cellular responses (downstream effect not directly

Ionotropic

   - agonists bind directly to and directly regulated the opening of an ion channel (ligand gated ion channel)

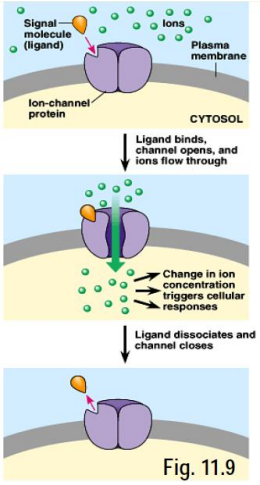


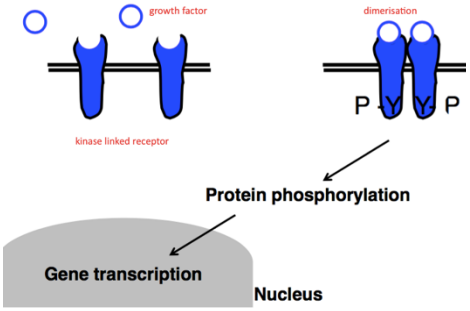
Fig. 11.9

Nicotinic receptor

   - ligand gated ion channel
   - 5 subunits located on skeletal muscle
   - agonist=acetylcholine (Ach)
   - Ach binds to a subunit causing a channel open
   - Na entry stimulates contraction

Kinase linked receptors

- Agonist binds to extracellular domain of a transmembrane protein
- This activates enzymatic activity of the proteins cytoplasmic domain
- Single helical transmembrane receptors either have an intracellular domain which contains intrinsic kinase activity (enzyme) or the intracellular domain is able to interact with cytosolic kinases (ligand binding that causes activation of the enzymatic activity of the receptor- phosphorylation of proteins)



e.g. Growth factor receptors

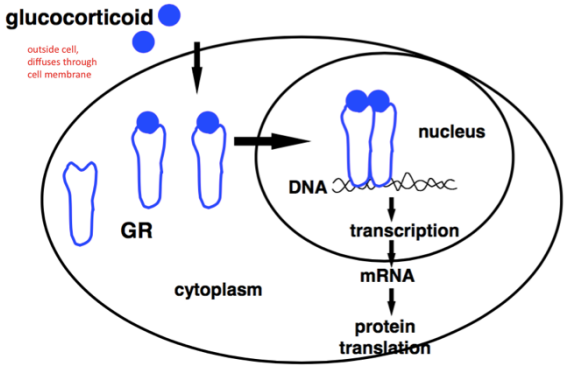
⇒ Agonist binding causes receptor dimerization

⇒ Activation of tyrosine kinase (cytoplasmic domain) phosphorylates substrates that regulate cell growth

⇒ Not a fast process because transcription needs to occur; relies on protein synthesis

Cytoplasmic (nuclear) receptor

- Located in the cell (drugs have to be able to get into the cell- lipid soluble)
- Lipid-soluble chemical signal enters cell
- Ligand binds to and activate intracellular receptor
- Receptor may regulate gene transcription
- Drug receptor complex enters nucleus and binds to DNA to induce or repress genes
- Slow onset- protein synthesis takes hours (have to alter protein synthesis)
- Effects last for days- slow protein turnover



e.g. Glucocorticoid receptor

⇒ Activation inhibits synthesis of cyclooxygenase

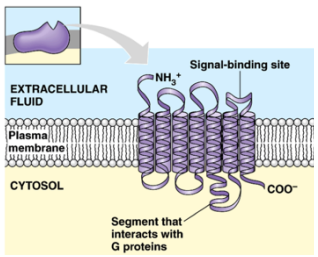
⇒ Glucocorticoid binds to receptor

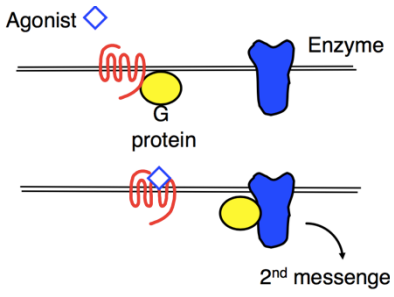
⇒ Dimerization of 2 receptors allows translocation of these receptors into the nucleus

⇒ At transcription you can get induction or repression of certain genes

G- protein coupled receptors (GPCR)

- Muscarinic AChR and adrenoceptors (a and b)
- Largest receptor family
- Agonist binds to cell-surface receptor consisting of 7 transmembrane segments (serpentine receptor)
- Extracellular binding site is where the drug is bound
- The intracellular segment tis that part that interacts with G proteins
- Linked to an effector protein by a G-protein (effector may be an ion channel or enzyme)
- It's not the binding that produces the response it's the triggering/coupling of G protein that produces a downstream effect
- GPCRs activate a particular G protein which is then able to selectively interact with the effector protein (e.g. ion channel or enzyme)
- Changes that activity of the 2nd messenger (or ion channel) that causes cellular modulation





e.g. muscarinic Ach receptor, adrenoceptors

⇒ Gs= stimulating protein, interacts with Adenylate cyclase which leads to an increase in cAMP

⇒ Gi= inhibitory protein, interacts with adenylate cyclase which leads to a reduction in level of cAMP

⇒ Gq= interacts with phospholipase C to increase IP_3 and DAG