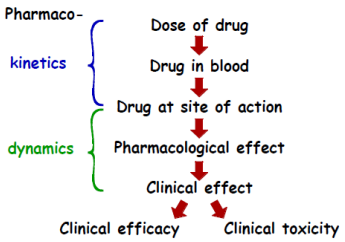
Lecture 1 - 3: Pharmacodynamics

Clinical dose-effect

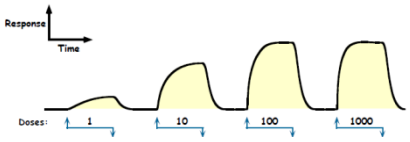


- ✓ Pharmacodynamics
  - Study of the molecular, biochemical, and physiological effects of drugs on cellular/body systems and their mechanism of action
- ✓ Pharmacokinetics
  - Study of the (fate) absorption, distribution, and elimination of drugs

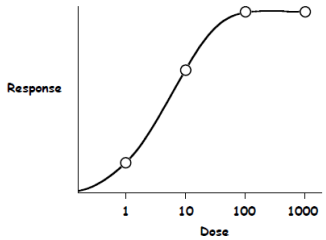
Both of these influence how much dosing you need

What is the right dose? - Enough to do some good

- ✓ Dose-response curve (in vivo)
  - Allows us to estimate:
    - Maximal response the drug can produce (E_{max})
    - Concentration or dose needed to produce 50% maximal response (EC_{50} or ED_{50})
    - Parameters that are useful for comparing the potencies of different drugs that produce qualitatively similar effects



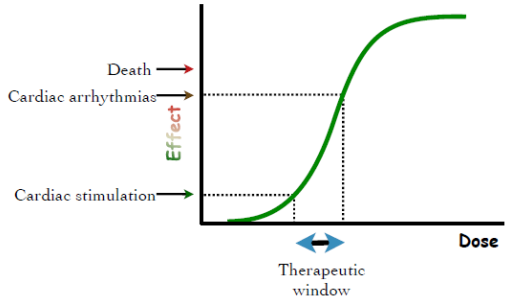
Increasing dosage increases the response. However, only up to a point where it no matter how much more you add will not give you any additional response (E_{max})



Sigmoidal curve (S-shaped)

What is the right dose? - Not enough to do much harm

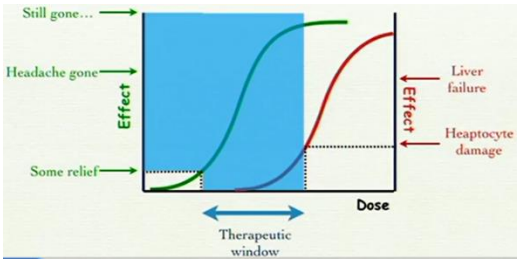
- ✓ Identical therapeutic and toxic mechanism
  - Same benefit and adverse target
  - E.g. Digitalis



In this example, the drug is used to treat patients with heart failure. They inhibit the NA-K-ATPase pumps which increases intracellular Na to promote Na-Ca exchange to increase myocardial contraction. However if you have too much then it will break down the membrane potential and cause adverse effects and death.

Therapeutic window *- enough dosage to do some good such that we don't get any adverse effects (poisonous)*

- ✓ Different therapeutic and toxic mechanisms
  - Paracetamol



You can keep increasing dose of paracetemol to relief your headache (green). However the adverse effects have a DIFFERENT dose response curve (red) - because it's a different mechanism.

Increasing paracetamol kills of endothelial cells in the lymphatic sinusoids via depletion of glutathione, which causes oxidation damage - liver dies

Prescribing note: *The usable dose of a drug is often constrained by unwanted actions*

Non-receptor targets for drugs

For a drug to have an effect in the body it must bind to a particular site (below)

- ✓ Ion channels
  - E.g. Ca2+ channels
- ✓ Enzymes
  - E.g. Cyclo-oxygenase
- ✓ Carrier molecules (transporters)
  - Serotonin uptake
- ✓ DNA
- ✓ Osmotic pressure
- ✓ Direct actions - Drugs actions that we don't understand

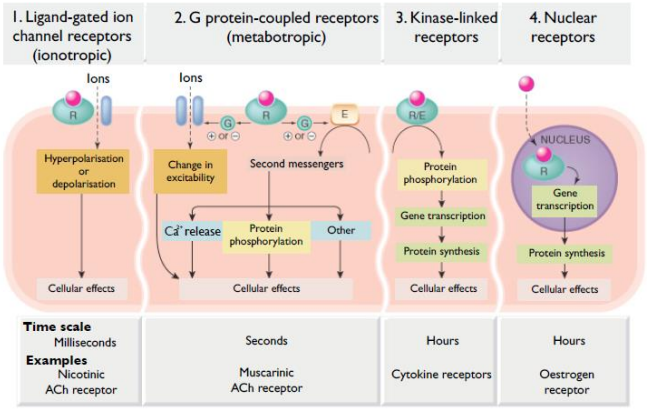
Receptors

- ✓ Receptors are the sites of action of
  - Neurotransmitters
  - Hormones (and autocoids)
    - Autocoids - also known as local hormones which are released and act upon the same/nearby tissue
  - Many second messengers
  - Many drugs

Local definitions

- ✓ A receptor is a biological macromolecule or complex that binds another molecule and initiates or modulates signalling or effector activity within a cell
  - Binding of endogenous ligands and some exogenous ligands results in activation of intracellular signalling pathways (signal transduction) - Efficacy
- ✓ A molecule that binds to a receptor is a ligand
- ✓ Ligand bind to binding molecules at binding sites

- ✓ A ligand that binds to a receptor and activates it is an agonist
- ✓ A ligand that binds to a receptor without activating it will act as an antagonist
- ✓ All receptors are binding molecules, but not all binding molecules are receptors



4 family of receptors

Receptor terminology

- ✓ Affinity
  - Tendency of a ligand (drug) to bind to the receptor
- ✓ Efficacy (intrinsic activity)
  - Tendency for it , once bound, to activate the receptor
  - Maximum effect = 1
  - No effect = 0
- ✓ Agonist
  - Have affinity and efficacy (mimics)
- ✓ Antagonist
  - Have affinity but no efficacy (prevents)

Receptor nomenclature

- ✓ Receptors are often named for the earliest known activator
  - Muscarinic receptors are activated by muscarine
- ✓ Receptors are also named from their cognate hormone or neurotransmitter
  - Muscarinic and nicotinic receptors are cholinoceptors or acetylcholine receptors
  - Adrenoceptors are activated by adrenaline and noradrenaline
  - Angiotensin receptors are activated by angiotensin

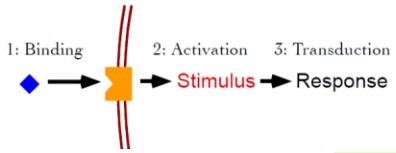
Receptor classes

- ✓ Muscarinic receptors (GPCR) and nicotinic (Ion channel) receptors are separate classes of ACh receptor (and unrelated types)
  - They only share the same neurotransmitter
- ✓ α-adrenoceptors and β-adrenoceptors are separate classes of adrenoceptor

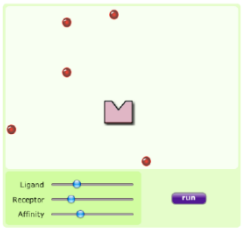
Receptor subclasses

- ✓ Muscarinic M1, M2, M3, M4, M5 receptors
- ✓ Nicotinic N_M on muscles, N_N in autonomic ganglia and CNS
- ✓ α_1-adrenoceptors on most blood vessels
- ✓ α_2-adrenoceptors on some nerves
- ✓ β_1-adrenoceptors predominate in the heart
- ✓ β_2-adrenoceptors on bronchi and some blood vessels

Three steps to response



Receptor activity starts with binding



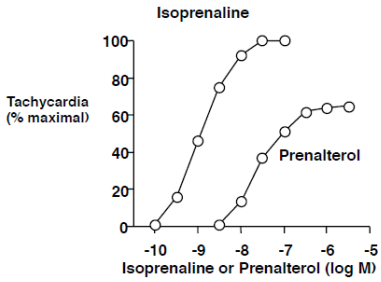
- ✓ To increase binding
  - Increase drug concentration
  - Increase receptor concentration
  - High drug affinity to receptor
    - Affinity property is a pair - between the receptor affinity for the drug and the drugs affinity for the receptor

Meet some agonists

Drugs with similar chemical structures have similar activity, as they fit into the same receptors

1. Isoprenaline (isoprenalterol)
   - β_1 and β_2 agonist
   - Full agonist
   - Highly potent
2. Prenalterol
   - β_1 selective
   - Partial agonist (max response 70%)
   - 30-fold less potent

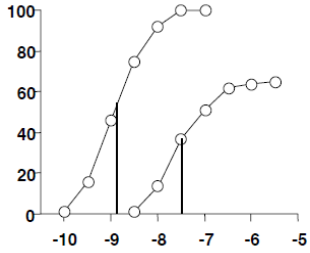
Agonist characterisation

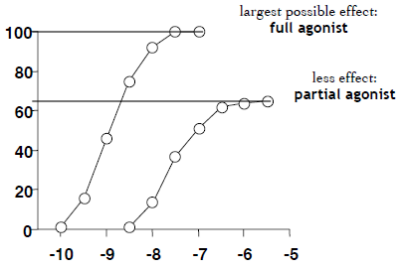


Concentration-response curves in rat right atria

Agonist potency

- ✓ EC_{50} or (the –ve log of EC_{50}) pD_2 is the measure of agonists potency
- ✓ Tells you the concentration that is required to produce 50% of the maximum response
  - The lower the EC_{50}, the greater the potency
  - Higher the pD_2, the greater the potency
- ✓ This can be calculated by measuring across from the 50% mark on the concentration-response graph and reading off the concentration
- ✓ Drugs of high potency generally have a high affinity for the receptors and thus occupy a significant proportion of the receptors even at low concentrations





It is important to note that dose-response curves cannot be used to measure the affinity of agonist drugs for their receptors, because the physiological response produced is not, as a rule, directly proportional to receptor occupancy

Partial Agonists

- ✓ Some agonists, although showing full receptor occupancy, do not elicit a maximal response-these are referred to as partial agonists
- ✓ While they have affinity, their efficacy is <1 in contrast to the full agonists whose efficacy = 1
- ✓ Partial agonists can act as antagonists to full agonists

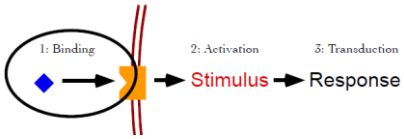
Well-known partial agonists

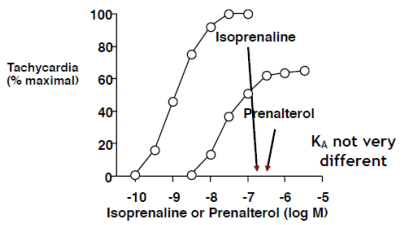
1. Salbutamol - Ventalin
   - β_2-adrenoceptors
2. Buprenorphin
   - Opiate receptors
3. Sumatriptan
   - 5-HT1 receptors
4. Pindolol
   - β-adrenoceptors

Not every receptor does desensitization (down regulation of receptors) but if they do, usually a strong activation of the receptor will cause more desensitization than a weak activation receptor - therefore partial agonist tend to do it less than full agonists

Why are Isoprenaline and Prenalterol different?

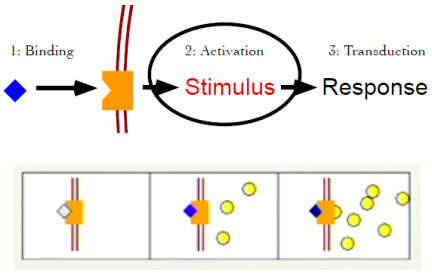
Three steps to response - Difference in the first 2 steps (either one or both)





Looking at binding first - they both bind to the β_1-adrenoceptor, but isoprenaline has slightly higher affinity. It's not very much higher to account for the 30-fold in potency.

- ✓ K_A is the equilibrium dissociation constant
  - Measure of affinity (but can't be determined from these concentration curves)
- ✓ A drug present at K_A will occupy half of the available receptors (K_A is affinity)



Looking at stimulus - These are 3 ligands that bind to a receptor with the same affinity. But #1 does nothing, #2 does something, and #3 gives a larger response. So these ligands differ in the ability to generate a response (yellow balls). This is a property of the ligand called efficacy - which is independent of affinity.

Efficacy

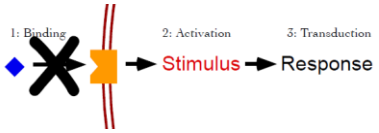
The ability of a drug to do the right thing

- ✓ Pharmacological efficacy
  - The strength of the receptor activation
    - Full agonists - high efficacy
    - Partial agonists - low efficacy
- ✓ Clinical efficacy
  - The strength of the beneficial effect
    - Full or partial, it depends...

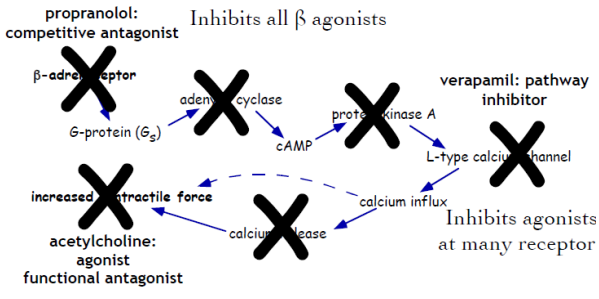
Antagonism

- ✓ Competitive antagonists
- ✓ Non-competitive (not at receptor)
  - Pathway inhibitors
  - Functional (physiological) antagonists

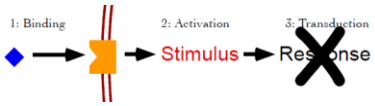
Competitive antagonism



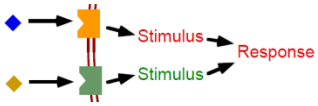
Non-competitive antagonism - Pathway inhibition



Functional or physiological antagonism - Non-competitive-antagonism



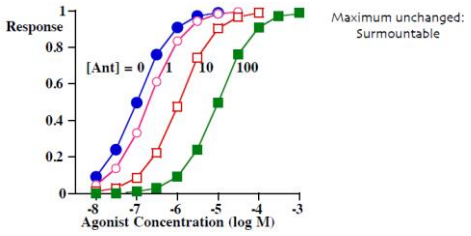
✓ E.g. Acetylcholine antagonism of adrenaline in heart



So in the example above, we have 2 ligands that activate 2 different receptors that stimulate different pathways to give OPPOSITE physiological responses. There is no competition of the ligand as they are both activated. The response will be based on the level of activation of each of the pathways.

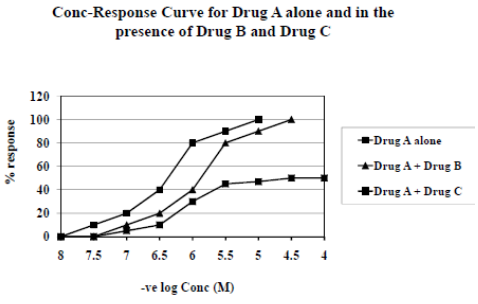
Surmountable antagonism

- ✓ In the presence of a competitive antagonist, the agonist occupancy at a given agonist concentration is reduced, because the receptor can accommodate only one molecule at a time
- ✓ However, because the two are in competition, raising the agonist concentration can restore the agonist occupancy (and hence the response)
  - The antagonism is therefore said to be <u>surmountable (overcome by increasing agonist)</u>



Competitive reversible antagonism

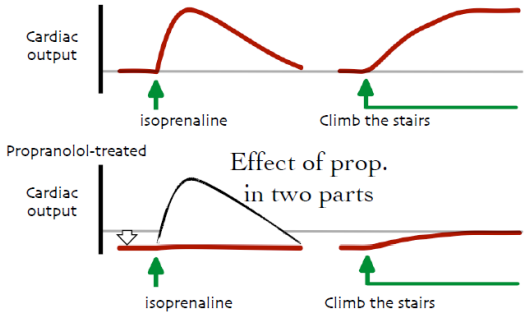
- ✓ Surmountable in the laboratory
- ✓ Often surmountable in vivo
  - Often not...
- ✓ Inhibits the actions ONLY of agonists that share their receptor
- ✓ Antagonist competes directly with the agonist for binding to the receptor
- ✓ Parallel rightward shift of the concentration-response curve
  - No depression in maximal response
  - Maximal response occurs at a higher agonist concentration that in the absence of the antagonist



Non-competitive antagonism

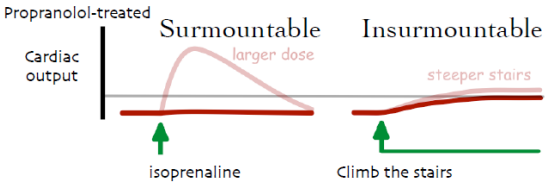
- ✓ Generally insurmountable
  - At least at high levels of antagonism
- ✓ Often less selective than competitive
  - Many receptors may share a pathway or response
- ✓ Do not bind to the same receptor as the agonist nor alter agonist-receptor binding
  - Not the same affinity as agonist
- ✓ Act by interfering with the cascade of events initiated by agonist-receptor binding
- ✓ Non-parallel rightwards shift of the concentration-response curve with depression in max response

Effect of an antagonist



In the top we have a pharmacological response and also a physiological response to increase C.O. When we put the drug (2nd diagram) we inhibit both responses as the drug blocks the receptors. However, in the physiological response we have some residual responses.

The moral of the story is that pharmacological intervention are simple. Whereas physiological responses are complicated and the residual output we see can be contributed to other responses other than the beta receptors (e.g. venous blood from leg muscles pumping back to the heart to increase stroke volume and C.O).



Antagonism summary

- ✓ Many sites at which agonist effects can be prevented
- ✓ Effect on agonist CRCs depend on mechanism of the antagonist and the efficacy (strength) of the agonist
- ✓ Antagonist potency is mostly determined by affinity
- ✓ Immediate effect depends on existing activation level

Allosteric Modulation

- ✓ An allosteric modulator is a substance which indirectly influences the effects of an agonist or inverse agonist at a receptor
  - They are not competing with the endogenous ligand to bind to its binding site

$GABA_A$ receptor

- ✓ These receptors are GPCRs and are mostly expressed in nerves
- ✓ The binding of GABA ligand will cause an increase in Cl^- polarization which will hyperpolarize the cell and decrease its excitability
- ✓ The receptors has 2 binding sites
  - GABA binding site
  - Allosteric binding site