Lecture 1 and 2

1. Explain what pharmacology encompasses and how it relates to other disciplines
2. Discuss the types of drug target and the factors that influence the binding of drugs to these targets
3. Describe how drug receptor affinity is measured
4. Explain how receptor theory models have evolved
5. Discuss the factors that influence the dose-response relationship
6. Explain the concepts of efficacy, partial agonists, and spare receptors

ONE

Definitions

Pharmacology: the study of the interaction of drugs within living systems

Drug: any chemical that affects living tissue

- Endogenous (internal substance)
- Exogenous (externally substance)
- Xenobiotic (foreign substance)
- Types:
    - Natural
    - Semi-synthetic
    - Synthetic
    - Genetically modified
- Nomenclature:
    - Individual name: chemical formula
    - Non-proprietary: generic
    - Proprietary: trade/brand
- Class
    - Therapeutic
    - Mode of action
    - Structure

Application: identify and develop therapeutics

Therapeutic: must be able to be administered and have an effect

- Dose-response
- Adverse effects
- Evidence-based
- Medical therapeutic:
    - Formulated to produce a therapeutic effect

Administration stages:

1. Drug release
2. Movement of drug from site of administration to target site (distribution)
3. Interaction of drug with target to produce desired effect

Study stages:

- Pharmacodynamics: how to drug causes its effects
- Pharmacokinetics: how to body reacts to the drug (metabolism and distribution)

TWO

Targets:

- Receptors
    - GPCR (Adrenaline= alpha/beta adrenoceptors/acetylcholine= muscarinic/nicotinic cholinergic receptors)
    - Nuclear/steroid receptors (oestrogen=oestrogen receptors)
    - Ligand-gated ion channel receptors (tyrosine=tyrosine receptors/acetylcholine= nicotinic receptors)
    - Kinase-linked receptors (cytokine= cytokine receptors)
- Enzymes
    - Ach esterase
    - Cyclo-oxygenase COX- NSAIDS
- Ion channel
    - Calcium/sodium channels- anaesthetics
- Transporter/carrier molecules
    - Noradrenaline
    - Na+
    - Serotonin transporters- SSRIs

Effects: for a drug to have an effect it must bind

- Specific/non-specific to tissue
- Drugs interact with specific molecular targets which determine the effect they produce
- Drugs can only mimic the biological actions of the cell, modulating (blocking or enhancing) the effect of endogenous components.
- No drug has complete specificity in its action and has varying degrees of selectivity
- Effect depends on:
    - Target (affinity and efficacy)
    - Number of targets interacted with
    - Where the targets are → how it gets there/what response occurs in same targets in different tissue

Drugs often resemble the natural ligands structure and binding depends on:

- Shape
- Solubility:
    - Ionisation
        - pKa of drug: depends on pH of target compartment
    - Size

Not all drugs interact with specific targets:

- Osmotic effects
    - Alters fluid balance between compartments
        - GIT: osmotic laxatives (magnesium citrate) which act as antidiuretics causing water to be moved into the gut and retained to treat constipation
        - Kidney: osmotic diuretics (mannitol): increased passing of urine by inhibiting water and sodium reabsorption. They increase pressure in renal tubules by causing retention of water

in the proximal tubule and descending loop of Henle. Used to prevent reduction in urine production during renal failure. Reduces intracranial pressure during a cerebral oedema.

- pH changes
    - Mylanta:
        - Contains magnesium hydroxide: $Mg(OH)2 + 2HCl <=> MgCl2 + 2H2O$
        - Used for acid reflux by neutralising acid
- Chelating agents (EDTA)
- Anti-cancer drugs

ACE Inhibitors:

Uses:

- Lowers BP
- Heart failure→ can remodel the cardiac muscle
- Has a protective effect on the kidneys in diabetics
- Coronary Artery Disease: reduced the risk of cardiac arrest (poor blood supply can cause arrhythmia/tachycardia/bradycardia= heart stops) or fatal myocardial infarction (heart attack→ blockage of the coronary artery and then the heart muscle dies)

Renin-angiotensin System:

1. Decrease in blood pressured causes release of renin from juxtaglomerular tubules of the kidneys
2. This triggers release of angiotensinogen from lungs
3. This becomes angiotensin I (no effect)
4. ACE found on endothelial cells, particular on the lining of the pulmonary system converts AI to AII by cleaving 2 amino acids from AI
5. Angiotensin II constricts blood vessels = increased BP
6. To stop increased BP, Captopril inhibits ACE. Bradykinin was also inactivated by Captopril

THREE

Affinity: ability to bind to a receptor

- Electrostatic
    - Hydrogen bonds
    - Ionic forces
    - Van der Waals forces
- Covalent

Selectivity: preference for one receptor over another, though the drug will bind to both

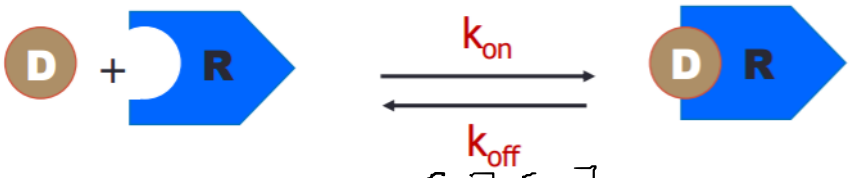
Efficacy: ability elicit a reaction once the drug binds

Binding:

- Reversible (non-covalent)
    - Drugs are only bound a receptor for a finite time = creates % drug bound
    -
- Irreversible (covalent)
    - Sometimes irreversible binding is not wanted for a drug because the only way to overcome it is to synthesis more receptors

Drug receptor binding

k_{on} = assoc rate constant
k_{off} = dissoc rate constant



- rate of association = $K_{on}[D][R]$
- rate of dissociation = $K_{off}[DR]$
- at equilibrium : rate of association = rate of dissociation

Rearrange……

- $\frac{[D]*[R]}{[DR]} = \frac{k_{off}}{k_{on}} = K_d$ = equilibrium dissociation constant *(units of concentration)*

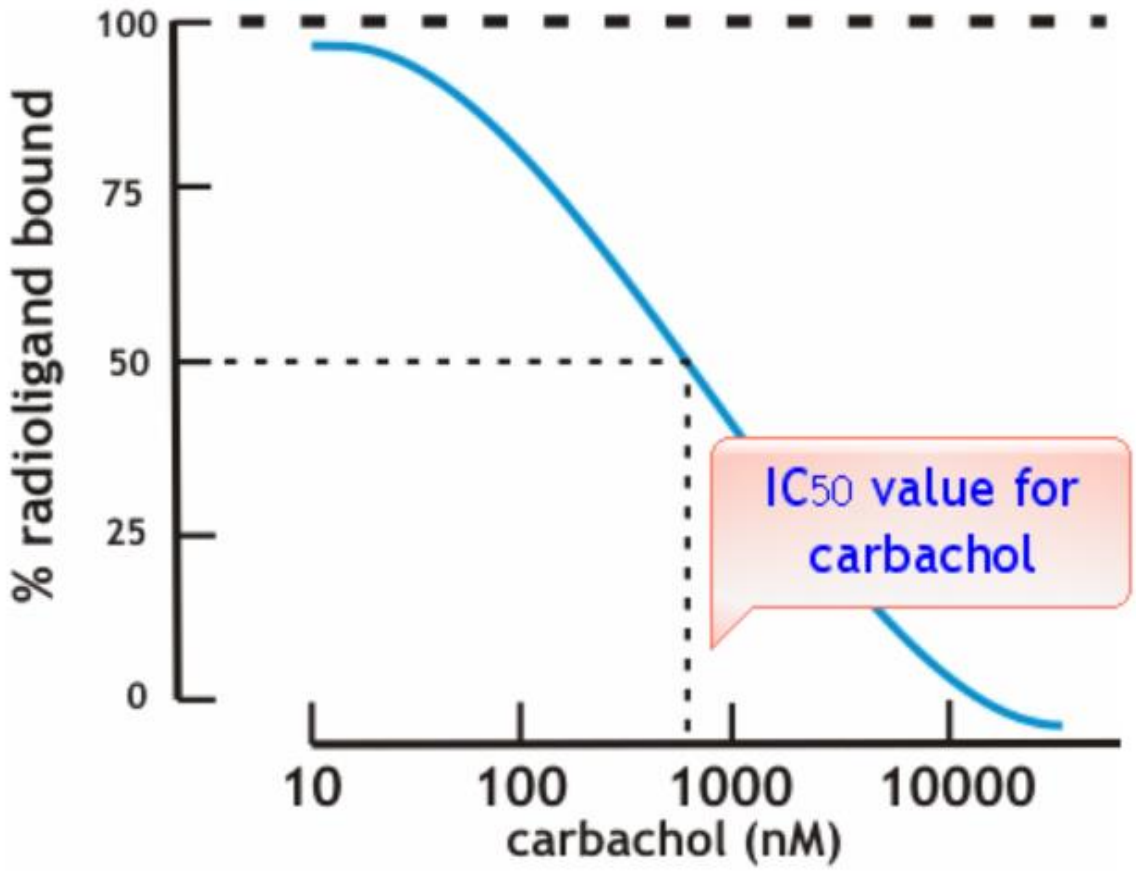
If 50% of receptors are occupied [R] = [DR] $\Rightarrow$ $[D] = k_d$

K_d = amount of drug required to bind 50% of receptors. Inversely proportional to affinity

Affinity is measured by:

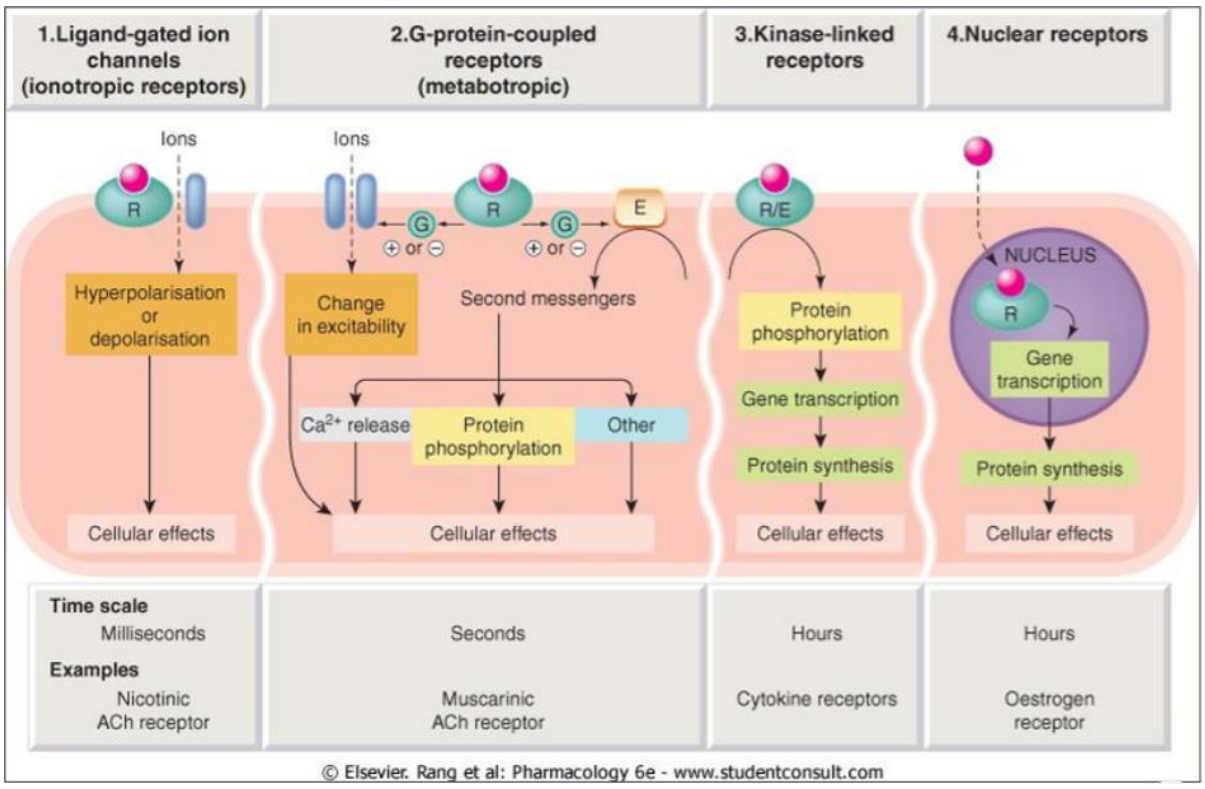
- Radioligands; ligands that have been tagged with a radioactive label. Radioligands are left to incubate in a receptor rich medium. To separate the unbound ligands from the bound ones, filters are used (as bound radioligands are larger). A Geiger counter is used to measure bound radioligand concentration.
- Competition binding (IC50): concentration of compound X required to cause 50% binding inhibition (inversely proportional to affinity).
    - Uses unlabelled compound X and labelled ligand

It can also determine receptor density: Bmax



FOUR

Receptors:



Agonist: increased reaction (affinity and efficacy)

Antagonist: no reaction (affinity but no efficacy)

Partial agonist: 100% saturation does not induce maximum effect: Emax (in the present of an agonist it acts as an antagonist)

FIVE

Dose-response reaction depends on:

- Law of Mass Action: effect depends on concentration
- Cures produced are put into log form so they are more easily analysed

EC50: Amount of drug required to elicit 50% response

- Measure of potency
- Inversely proportional to potency
- Shift to the left = more potent
- pEC50 = -logEC50 (proportional to potency)

Occupation Theory Models

Clarks Model: response determined by the proportion of receptors occupied by the drug

- Max response occurs with 100% saturation = linear relationship
- Implies:
    - Response is dictated by tissue not drug
    - All agonists have the same max response

Modifications:

- However, the above model is wrong. A highly efficient drug can cause 100% response without 100% saturation which leads to spare receptors.
- Spare receptors: receptors in excess of those needed to produce maximum response. Furthermore, not all agonists produce the same Emax.
- Some agonists cannot produce Emax with 100% saturation = partial agonsits
- Efficacy is determined by receptor density and drug efficacy.

Intrinsic efficacy: drug characteristic

Receptor and response coupling: tissue characteristic

SIX

Partial agonist: has efficacy and affinity, but efficacy is lower than a full agonist.

- Efficacy is determined by:
    - Conformational state of receptor
    - Interactions with more than once receptor to induce multiple effects.
    - Selectivity

Therapeutic Index

Window within which the drug causes its desired response without become toxic.