PHA2022

Pharmacology considers:

- Pharmacotherapy:
    - Drug-response relationship
    - Selectivity of action
    - Structure-action relationship

Lecture 1

1. Define the terms pharmacodynamics and pharmacokinetics
2. Describe (with examples) the non-specific ways in which drugs can produce therapeutic effects
3. Discuss the four specific molecular targets of drug action
4. Explain the importance of selectivity and how drugs can produce unwanted effects

ONE

Pharmacodynamics: how the drug acts on the body

- Non-specific
    - No targets
    - More side effects as it acts on a greater proportion of the system
    - Not efficient
- Specific cellular targets
    - Majority of drugs
    - Binding to particular cellular components causes a response
        - Involves: Van der Waal's
        - Hydrogen bonds
        - Electrostatic interactions
        - Covalent (irreversible) bonds
    - Molecular targets are usually proteins or DNA
    - Drug targets:
        - Ion channels
        - Enzymes
        - Transport systems/carrier molecules
        - Receptors
            - GPCR (Adrenaline= adrenoceptors/acetylcholine= muscarinic receptors)
            - Nuclear receptors (oestrogen=oestrogen receptors)
            - Ligand-gated ion channel receptors (tyrosine=tyrosine receptors/acetylcholine= nicotinic receptors)
            - Kinase-linked receptors (cytokine= cytokine receptors)

Pharmacokinetics: how the body acts on the drug (to move it through the system)

TWO

<u>Drugs</u>

- Simple
- Basic and inorganic
- Non-complex compounds
- E.g. Mylanta:
    - Contains magnesium hydroxide: $Mg(OH)2 + 2HCl <=> MgCl2 + 2H2O$
    - Used for acid reflux by neutralising acid
- E.g. Cheltaing agent:
    - 'Claw' molecule that 'mops up' heavy metal molecules

    - E.g. EDTA (ethylenediaminetetraacetic acid)
        - Big molecule with multiple binding sites for multiple chemicals (heavy metals)
- Physical processes:
    - Only applicable to a few drugs
    - E.g. osmosis: 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.
    - E.g. Surfactants: reduce surface tension
        - Simethicone: decreases pain associated with GI gas
        - GI gas is prevalent in babies or those suffering from indigestion

THREE

Protein Targets

Block endogenous factors via:

- Competition with endogenous ligands
- Selectivity: the ability for a drug to prefer one target over another
    - Depends on:
        - Structure
        - Size
        - Charge
    - Increased by:
        - Compartmentalisation
        - Changed structure
    - Reciprocal:
        - Classes of drug bind certain targets
        - Targets recognise certain classes of drug
        - E.g. Adrenaline targets both lungs and heart.
            - Salbutamol: prefers lungs as target
            - Dobutamine: prefers heart as target
    - Relative to:
        - Dose (increased dose = increased chance of interactions)
- Specificity: the ability for a drug to act with a single, particular target
    - Depends on the quaternary structure
- Ideally, drug only interacts with 1 target = 1 effect (specificity)
- In reality, drugs prefer one target over others (selectivity), but can act on more than one target

Ligands:

- Hydrophobic proteins attract hydrophobic ligands to form tight bonds
- Binding is aided by hydrogen bonds
- As well as pi-pi stacking between aromatic groups and ligands
- Pi-cation also bind ligands to proteins

Ion Channels

Control movement of ions into and out of the cells

- Hydrophobic cell membranes
- Ions: hydrophilic due to charge
- In all cells of the body

- Maintains voltage gradient and ionic flux
- Important in excitable cells (pacemakers/neurons)
- Gated:
    - Ligand (Ach nicotinic)
    - Voltage (Na^+)
- Action of drugs:
    - Block (e.g. local anaesthetic blocks nociception/pain)
    - Open (e.g. K^+ channel openers)
        - Hyperpolarises membrane
        - Increases speed of cell recovery
        - Blocks Ca^{2+} channels opening
        - Causes vasodilation = decreased blood pressure
        - E.g. Minoxidil
    - Modulate:
        - Increase or decrease chance of opening
        - E.g. Valium (anti-anxiety)
        - Increases frequency of Cl^- channel opening which is enhanced by GABA
            - GABA: inhibitory neurotransmitter in the CNS = calms nervous activity
            - Barbiturates and benzodiazepines

Enzymes

Biological catalysts: increases rate of reaction to sustain life

Drugs can:

- Inhibit enzyme activity
- Inhibit substrate activity
- Competitively bind

Prostaglandins: mediators of pain and inflammation

- Inhibited by aspirin and ibuprofen (prevents mediator from being made)
- Sarin (prevents mediator being broken down): nerve gas/insecticides
- Precursor arachidonic acid is converted into prostaglandins via cyclooxygenase (COX)

Acetylcholine→ broken down by Ach esterase = inactivates metabolites

Carrier Molecules

Actively transports substances across membranes (against concentration gradient)

- Transporters
- Symporters
- Antiporters
- Noradrenaline uptake terminates action
    - Cocaine blocks NA uptake = prolonged effects of NA
    - Amphetamine (speed up workings of the brain: Ice) blocks NA uptake and increases NA release from inside cell

Receptors

Targets:

- Neurotransmitters
- Hormones
- Present in:
    - Membrane

- Cytoplasm
- Nucleus

Affect:

- Agonist (increases response): mimics endogenous ligands
- Antagonist (decreases response): blocks endogenous ligands

FOUR

Side-effects:

- Arachidonic acid (precursor of prostaglandins) is converted via COX and mediates pain/inflammation. COX also mediates protective lining of the stomach
- If COX is block, so is pain, but stomach ulcers may form

This is why selectivity is important

Lecture 2

1. Explain the terms potency, affinity and efficacy
2. Use these terms to compare and contrast full agonists, partial agonists and antagonists
3. Discuss how the differences between competitive reversible and irreversible antagonism can be demonstrated experimentally
4. Give examples of clinically important drugs which act as agonists or antagonists

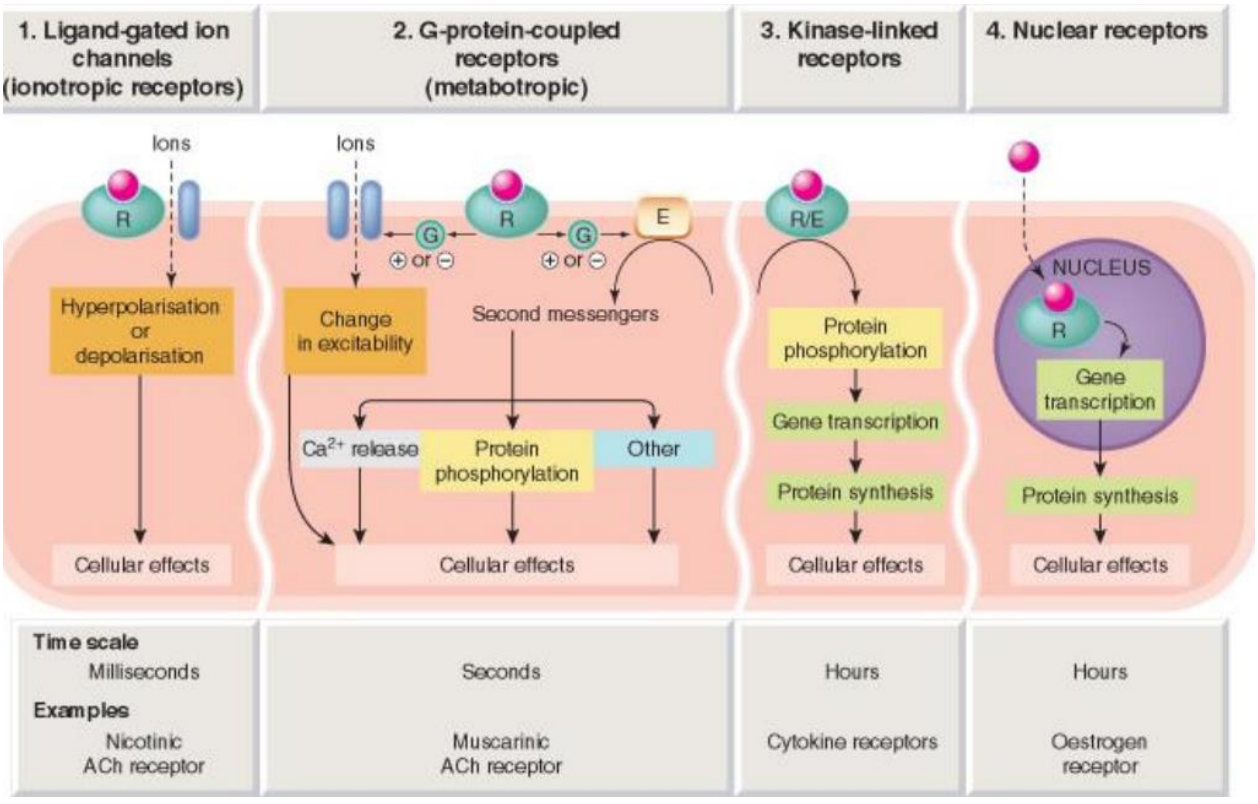
<u>Receptors</u>

Mediators:

- Neurotransmission
- Hormones

Present in:

- Cell membrane
- Cytoplasm
- Cell nucleus



Adrenoreceptors:

Alpha 1 is located on:

- All vascular smooth muscle, although densities vary throughout the body→ vasoconstriction
- GI & urinary sphincters→ constriction
- Dilator muscle of the iris
- Arrector pili muscle of hair follicles

Alpha 2 is located on:

- Secretory terminals of some postsynaptic neurons (increases NA secretion)
- Secretory terminals of some presynaptic neurons (decreases NA secretion)

Beta 1 located on:

- Cardiac pacemaker→ increase heart rate
- Myocardium→ increase CO force
- Salivary gland ducts→ decrease salivation
- Eccrine and apocrine sweat glands→ increase secretion

Beta 2 is located on:

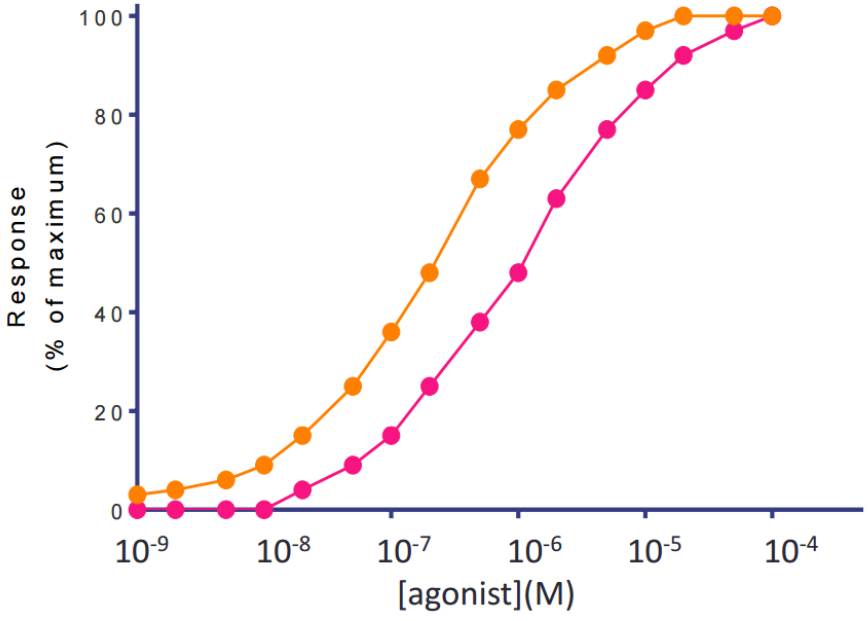
- The gastrointestinal tract→ relaxation
- The urinary bladder→ relax
- Skeletal muscle arteries→ dilate
- The bronchial tree→ bronchodilation
- Some coronary vessels→ vasodilation

Lock and Key:

- Key might not fit lock
- Key fits but does not turn (antagonists = affinity but no efficacy)
- Key fits and turns (agonist= affinity and efficacy)
- Affinity: how well a drug binds to the receptor
    - Different to selectivity: how much a molecule prefers binding to one receptor over another
- Efficacy: how well a drug elicits a response once bound to the receptor

ONE

The Drug:



- Follows a sigmoidal curve
- As the concentration of the drug increases, so too does the response until it plateaus
- EC_{50}= potency.
    - Point at which the drug elicits 50% of its response
    - Increased EC_{50} (shift to the right) = decreased potency
- Potency: relates to the amount of drug required to produce a particular effect

- Chance in potency due to shift to the right.
- Change in concentration
- Chance in response at a particular concentration

Lignocaine: blocks Na^+ channels (anaesthetic)

Cocaine: blocks NA uptake

Sarin: blocks Ach esterase (nerve gas)→ stops Ach (neurotransmitter of the nervous system) breakdown

- Cholinesterase inhibitor

Aspirin/ibuprofen: blocks COX

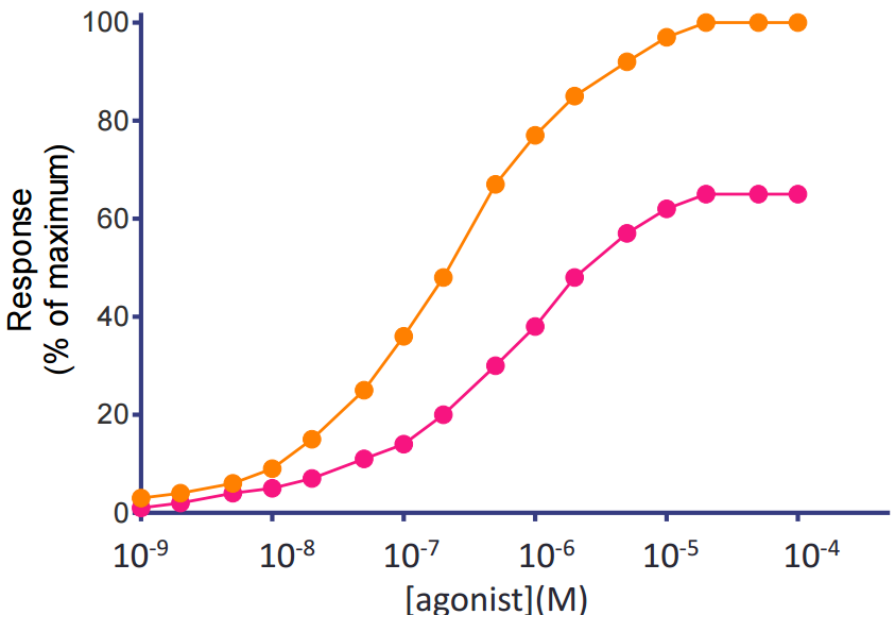
EDTA: heavy metal chelator

Ligand is the first messenger for nuclear/steroid receptors

Adrenaline acts on α/β receptors

Maximum effort: how well a drug elicits a response

- How good the agonist is
- Measure of efficacy
- Comparison



The decrease in maximum response indicates less efficacy and a partial (less effective) agonist.

TWO/FOUR

Full agonist: does not require full saturation to elicit 100% response

Partial agonist: does not always produce 100% response

- May require more receptors

Agonists:

- E.g. Ventolin (salbutamol): stimulates β-adrenoceptor
- Morphine: opioid receptor
- Adrenaline: adrenoceptor

THREE/FOUR

Antagonists

Competitive antagonism:

- Antagonist occupies site but generates no response
- Antagonist occupies site so agonist cannot bind
- NO efficacy
- Can be reversible or irreversible depending on the type of binding:
    - Covalent (irreversible)
    - Hydrogen/van de Waal's/polar (reversible)

Non-competitive antagonism

- Physiological:
    - Have opposing effect
    - Contraction vs. relaxation
- Chemical:
    - Inactivates
    - Antacid
- Pharmacokinetic
    - Affects concentration at compartmentalised sites
- Allosteric
    - Causes changed conformation so agonists cannot bind
    - Stimulates second messenger
- Narcan (naloxone)- μ- opioid receptor
- Claratyne (loratadine)- histamine receptor