Fundamentals of Pharmacology

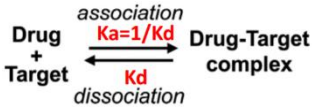
Receptors function in pharmacology

Pharmacokinetics – what the body does to the drug

Pharmacodynamics – what the drug does to the body

Receptors determine the quantitative relationship between dose/ concentration and pharmacological effect: ↑ receptors, ↑ effect.

Receptor binding sites contain amino acids which increase strength and specificity of ligand binding (individual differences is drug responses can be due to genetic mutations in receptor m/c).



Law of mass action – the rate of reaction is proportional to the concentration of the drug and the concentration of the receptors.

Kd – dissociation constant. Drug-receptor complex is at equilibrium with unbound drug and receptor; Kd is the concentration of free drug is at half-maximal binding (i.e. at equilibrium)

Low Kd value – stronger ligand/receptor bond.

Receptors are also responsible for selectivity of drug action and the pharmacological effects of drugs.

Targets for drug action can be: receptors, ion channels, enzymes, transporters.

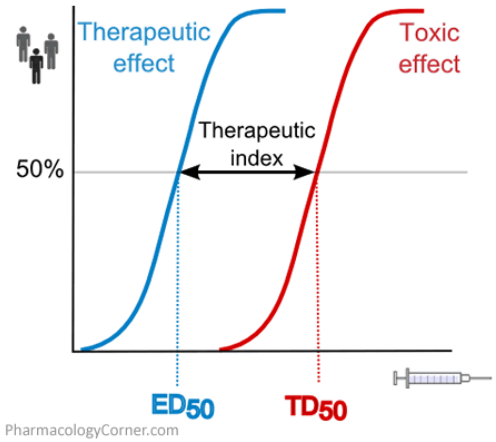
The binding of a drug to a receptor is determined by the forces: Ionic bonds, hydrogen bonds, hydrophobic interactions, Van Der Waals forces (dispersion forces) – in order of decreasing strength. These forces are reversible, aside from covalent bonds.

Covalent > Ionic >Hydrogen > Van Der Waals

Properties of receptors:

Recognition - receptor must exist in a conformational state that allows the binding of the substrate.
Saturability – receptors exist in finite amounts.
Reversibility – binding must be non-covalent so it can be reversed.
Stereo-selectivity – receptor should only recognise one naturally occurring stereoisomer.
Agonist specificity – structurally related drugs should bind well and poorly related drugs should bind badly.
Tissue specificity – binding should occur in tissues that are sensitive to the drug.

ED50 – median effective dose – the dose that produces 50% of the biologically observed effect.
EC50 – Concentration of drug which gives half of the maximal response.
Emax – max. response an agonist can produce in a tissue (crude measure of efficacy).
Efficacy – ability to produce a desired or intended response -the strength of a response produced by an agonist.
Drug is more **efficient** if the maximum effect is higher.
Drug is more **potent** if the maximum effect is reached at lower doses. **(Amount of a drug that is needed to produce a given effect).**



Therapeutic index – a comparison of the average dose that causes therapeutic effect compared to the average dose that produces causes toxicity. This is dependent on the drugs chemical stability, solubility, metabolic stability, absorption, excretion, biological activity. Therapeutic index is a guide only, other things can affect the safety of drugs such as age, pregnancy, disease states etc.

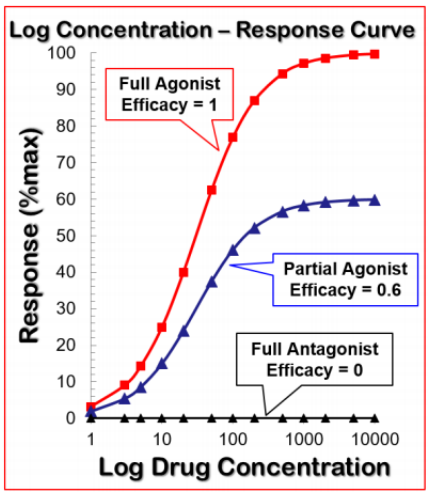
Ligand – generic name for all m/c that bind to receptors.

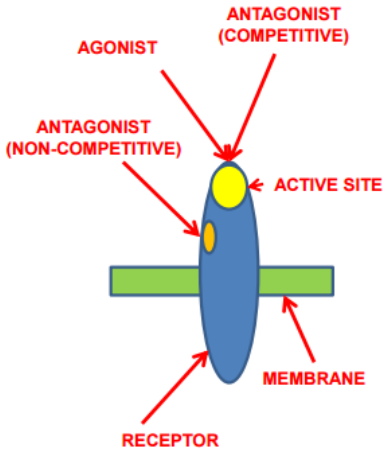
Agonists – m/c that activate the receptor.

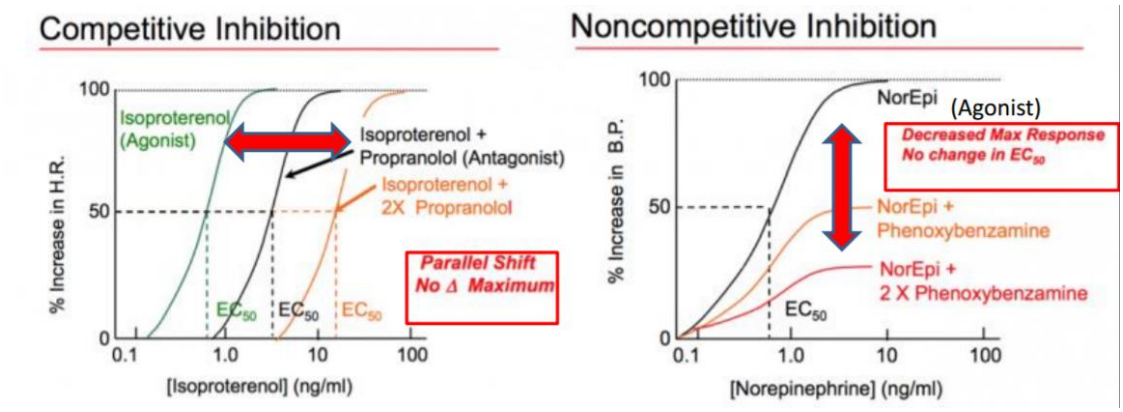
Antagonist – bind to the receptor and block its action.

Competitive – binds to active site.

Non-competitive – binds to site on receptor other than the active site.







Ion channels and GABA

- → **Phenytoin**
- → **Diazepam**
- → **Phenobarbital**
- → **Flumazenil**

4 major types of receptors:

1. Ion channels
2. G-protein coupled receptors
3. Tyrosine kinase coupled receptors
4. Intracellular receptors

Function of ion channels:

- → Transfer small m/c b/w cells
- → Control release of neurotransmitters and hormones
- → Initiate muscle contraction
- → Control the generation, conduction and transmission of electrical signals in the nervous system.

Ions are unable to diffuse across the hydrophobic barrier of the lipid bilayer – they require an ion channel, which transport ions down the concentration gradient. Ion pumps use energy (ATP) to transport ions against their concentration gradient.

Ion channels are selectively permeable to specific ions. They are 'gated' and their opening is regulated by: voltages across the cell membrane, ligands, mechanical stimulus and phosphorylation.

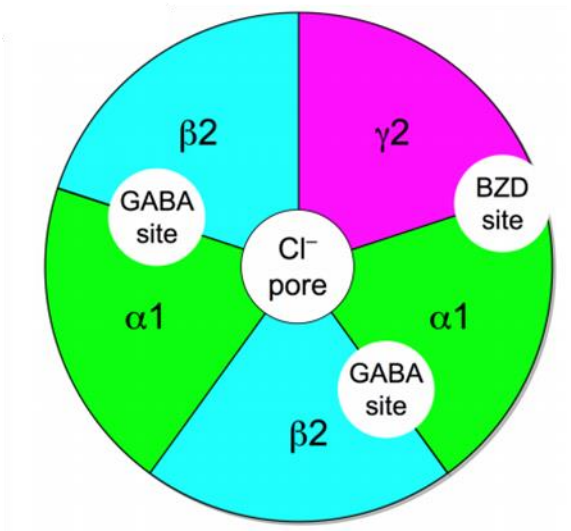
Phenytoin → sodium channel blocker. Binds to sodium channels, inactivating them, therefore blocking the propagation of electrical impulses across the synapse of nerve cells. Phenytoin is an anti-seizure agent (non-sedative).

GABA (Gamma aminobutyric acid) receptors:

- Inhibitory neurotransmitter of the central nervous system. GABA binds → opens Cl- pore → hyperpolarises cell → harder to depolarise and
- **GABA-A receptors regulate Cl- ligand-gated channels.**
- GABA-B receptors are G-protein coupled receptors.

GABA-A receptors/channels:

- Composed of 5 different subunits arranges around a central pore (where Cl- moves through).
- The GABA neurotransmitter/ligand binds and causes this receptor to open.
- GABA binding causes a change in GABA-A receptors conformation, opining the Cl- pore.
- Influx of Cl- into the neuron causes hyperpolarisation of the neuron, reducing its activity as it makes it harder to depolarise the neuron to reach an action potential to propagate a signal.



GABA agonists – bind to the active site (where GABA binds)

Antagonists – compete with GABA for the binding site and therefore inhibit its action.

→ **Bicuculline** – Inhibits inhibitory neurotransmitter, therefore results in too much activation of the nervous system, mimics epilepsy.

Positive allosteric modulators – bind to allosteric sites on the channel causing an **increase in the receptors action**. Binding causes a conformational change of the receptor, **increasing the affinity of agonists for the active site**.

→ Benzodiazepines, Barbiturates, Alcohol – Supress the nervous system.

Allosteric – site other than the active site

Negative allosteric modulators – binds to an allosteric site, decreasing the action of the receptor when an agonist is bound to the active site.

→ **Flumazenil** – Decreases the action of the GABA-A receptor. Competitive inhibitor of the BZD active site, used in benzodiazepine overdose.

Many drugs bind to receptors on the GABA-A channel. They bind at sites other than the GABA binding site and increase the strength of GABA's binding to its own site. Therefore, enhancing the effect of GABA on the central nervous system which is inhibition (**GABA is an inhibitory neurotransmitter**).

These drugs include:

→ **Phenobarbital** – a sedative
→ **Diazepam** – known as Valium, an anti-anxiety drug

Due to their common action of **supressing the nervous system**, when taken together and in the presence of alcohol they will have an additive supressing effect which can result in over suppression of the CNS and respiratory failure as an example.