BIOM2052 – Lectures 1-4

Drug Receptors
Drug receptors and drug targets
Receptor classification
General mechanisms of receptor classes

Mechanisms of drugs can be broken into two separate groups – **pharmacodynamics** (how it affects the body; receptors, enzyme targets, membrane channels – **properties** of the **drug**) and **pharmacokinetics** (how the body affects the drugs; absorption, distribution, metabolism, excretion – **properties** of **drug target**).

Endogenous **ligands** are those of internal origin (of the organism) and attaches to endogenous receptors like a key and lock. Ligands bind to receptors, whose function is to recognize and respond to endogenous signal. Other molecules that drugs may target are known as drug targets.

Specificity is reciprocal – drugs bind certain targets; targets recognise certain drugs. No drugs are completely specific – increase dose will affect other targets.

Agonists activate target receptor – antagonists block target receptors. There are four types of receptor/drug targets:
Enzymes – largest class that are targeted.
Transporters – membrane associated proteins that transport molecules from one side to the other.
Ion channels – important in CNS allows movement of ions across membrane.
Signalling proteins (receptors) – cell surface receptors and intracellular proteins that signal to one another through domino effect.

Enzymes as drug targets
1. Use an **inhibitor/antagonist** to inhibit normal actions of enzyme.
2. Use **false substrate** as opposed to endogenous ligand to produce an **abnormal metabolite**.
3. Use a **prodrug** (no effect themselves) to be activated by the enzyme, producing the **active drug**.

Transporters
1. **Inhibitor** blocks transport directly on the site of binding or indirectly within membrane.
2. **False substrate** transport results in **accumulation** of abnormal compound.

Ion channels
1. **Blockers** prevent permeation through channel.
2. **Modulators** alter the probability of opening.

Receptors
1. **Ligand-gated ion channel**
5 transmembrane units – ligand binds to protein, causing it to open up allowing ions to flood in and **hyperpolarisation/depolarisation** and cellular effects to occur. Example – Ach binding to nicotinic receptor. **N/C terminals** are on the same side.

2. **G-protein coupled receptor**
Largest group (85% of drugs target) – ligand binding to receptor activate multiple pathways within the cell (change in excitability or second messengers). **7 transmembrane units.**
Resting state – **GDP** present on receptor (**alpha subunit)** binds two other subunits (**beta and gamma**).
Receptor occupied by agonist – **alpha subunit** separates from **beta and gamma subunits**. An extra **phosphate** binds to GDP to become **GTP → GTP** activates **target 1** whilst **beta/gamma** activates **target 2**.

Return to rest – **GTP** loses 1 phosphate molecular to become **GDP**, shutting down T1. Beta/gamma shuts off T2 and returns to bind GDP at the receptor, returning to resting state. **N/C terminals** opposite side.

3. **Kinase-linked receptor**
A kinase is an **enzyme** that adds **phosphate** onto a protein – **phosphorylation** and **de-phosphorylation** are key within the cell. **Ligand** binds receptor causing **cascade of protein phosphorylation** via kinase, resulting in cellular effects. **N/C terminals** opposite side. Example – Insulin binding insulin receptor; 2 alpha and 2 beta units.

Kinase can only phosphorylate 3 types of amino acid – tyrosine, serine or threonine. Key is the sequential activation via phosphate one molecule at a time resulting in **gene transcription**.

4. **Nuclear receptor**
Receptors sit in cytoplasm bound to accessory proteins. Ligand binds receptor causing accessory proteins to fall off and receptor to migrate into nucleus, activating target genes. **No membrane**.

Dose-response relationships
Dose-response curves
Partial and full agonists
Potency and efficacy
Therapeutic window and index

Binding of drugs to receptors follows the **Law of Mass action**. At equilibrium, **receptor occupancy** (i.e. **effect**) is related to **drug concentration** and its **affinity** for the receptor. Higher the affinity, the lower the concentration required to produce a level of occupancy.

The **dose-response curve** demonstrates how with increasing concentration drug [A], eventually the maximal response plateaus. The curve is converted to log[A] to demonstrate the effect of drug over many orders of magnitude. The **point of inflection** occurs at **EC50** – the **effective concentration at 50% maximal effect**. The **slope** informs us of the dose range between no effect and maximal effect – steep slope = higher risk of toxicity; wide slope = difficult to achieve maximal effect.

How well the drug binds to receptor is known as **affinity**. How efficiently the receptor translates binding to effect is known as **efficacy**.

Potency is indicated by left/right shifts on a log[A] graph. The more rightward it shifts, the less **potent** the drug is – since you would need more of the drug to achieve the same levels of effect. **Efficacy** is independent for drugs – it is indicated by the amount of agonist required to achieve **EC50** and determines how efficacious a drug is (dose required for response).

There are four classes of "antagonists":
1. **Competitive** antagonists compete with endogenous ligand at active site of receptor. Adding competitive antagonist shifts the curve to the right, since there are now two drugs competing for the same site of the receptor resulting in a decrease in **potency**. These are **reversible antagonists**.
2. **Pseudo-irreversible antagonists** have extremely high **affinity** (strongly competitive) with the target site, taking a long time to come off – these antagonists effectively reduce the number of receptors available for endogenous ligand to attach to, decreasing the **maximal effect** and therefore, lowering **efficacy**.
3. **Allosteric modulators** bind far away from the active site; however they modulate receptor activity via signalling. It can be either antagonistic or synergistic (negative/positive modulation).
Negative allosteric modulators are also known as **non-competitive antagonists**. Both **competitive** and **non-competitive** antagonists are **pharmacological antagonists**, since they revolve around altering the endogenous receptor.

4. **Functional antagonists** are drugs that bind are different receptors but have opposite functions to each other also known as **physiological antagonist**.

Partial agonists demonstrate **partial effect** of a **full agonist** – their Emax plateaus earlier.

The **therapeutic window** is the drug range between good response and minimum toxic response. The **therapeutic index** measures the drug concentration ratio between **TD50 (toxic dose)** over **ED50 (effective dose)**. **Toxicity** is defined as the receptor doing something that we **don't want it to do**, toxicity curve is shifted to the right of the dose curve as a separate curve. The more right-shifted, the safer the drug.

Two state receptor model
Two state receptor model
Inverse agonists
Allosteric mechanisms
Biased signalling
Cooperativity

Two state receptor model states that some receptors exist in either **resting** or **active state** which are in **equilibrium.** The active state can elicit a response even in **absence of drug**. Having a drug bind the receptor (in **active state**) causes **effect** and since less active state receptors are present, shifts the equilibrium toward the **active state** (less resting state). Resting ←→ Active → Response

Agonists bind to the active state causing greater response. **Inverse agonists** bind to the resting state, shifting receptors existing in active state to the left and **decreasing response**. Therefore, different drugs can either increase or decrease activity through the **same receptor**. An **antagonist** binds equally between the two and therefore does not affect equilibrium or alter the response.

Therefore, on a graph, having only antagonist present would be the same level of activity as if there were no drug. Having agonist increases activity and having inverse agonist decreases activity due to changes in resting state/active state equilibrium. An antagonist also shifts the curve to the right equally for both agonist and inverse agonist since it binds equally to both resting and active states.

Partial agonists have **affinity** for **both states** of receptor, thus it activates like a full agonist but also inactivates at the same time. The net effect always has a lower maximum effect – and the same holds true for **partial inverse agonists**.

Allosteric modulators bind to areas of receptor different to endogenous ligand and modulates the receptor – positively or negatively. For instance, a cationic substance can bind to a highly negative membrane region and thus modulate the calcium channel effect within it. Ba^{2+} alters nicotinic receptors ability to open/close, increasing sensitivity from a different receptor than the endogenous ligand (Ach). Importantly, ligand must still be present since allosteric only alters ligand binding and has no effect on its own. A neutral allosteric ligand does nothing.

Receptors can signal through multiple pathways – we can synthesise different drugs that engage the same receptor for different outcomes known as **biased signalling** and is determined by molecules within the cell.

Cooperativity occurs when a receptor contains multiple binding sites not independent of one another. **Allosteric cooperativity** can be positive or negative. **Configurational cooperativity** makes use of a polyvalent ligand (tether two drugs together), where having one drug bind improves likelihood of second binding due to proximity.

Application of drug receptors to practical pharmacology
Spare receptors
Desensitisation
Application of drug receptors in dentistry

Not all maximum responses require **maximum receptor occupancy**. Activation of a small proportion can produce max effect – those that aren't activated are known as **spare receptors**. **Bottlenecking** of **downstream signalling** (less B receptors than A receptors) means that there is not a direct relationship between drug interaction and ultimate effect.

Desensitisation is the loss of activity that occurs with repeated exposure to drug – also known as downregulation, adaption and tolerance. It can be the result of:
1. Change in receptors – cell doesn't want any more ions coming in so channel changes shape or gets bound to another protein, no longer opening upon attachment of ligand.

2. Translocation of receptors – cell-surface receptors **internalise** (switch off cell) when bound by ligand, decreasing number of receptors on cell surface. Having spare receptors means less desensitization as maximal effect can still be achieved by subsequent additions of drug (since there are spares that aren't translocated). Internalisation results in receptor being recycled.

3. Exhaustion of mediators – result of chronic exposure; presynaptic cell activates releasing neurotransmitter into synaptic cleft (dopamine) → affects dopamine receptors postsynaptically that eventually **diffuses away** (smaller pathway) or **transported** by presynaptic vesicles to be recycled. Cocaine blocks transporters preventing recycling of dopamine increasing amount of time dopamine spends in cleft and greater effect of dopamine. Consequence is overstimulation postsynaptically and desensitization (pathways 1 and 2). This increases the amount of dopamine that diffuses away → not refreshing presynaptic stores of dopamine decreasing mediators. Since there are less mediators, the future effects will be less strong.

4. Change in drug metabolism – the more the liver is exposed to carbamazepine, the faster the drug is metabolised; basically desensitization as the result of body getting rid of it faster.

5. Physiological adaption – body adapts to drug-induced changes by altering homeostasis: diuretic block sodium reabsorption and increases water excretion, lowering BP → activates renin-angiotensin → increases water retention through aquaporin → increases blood pressure.

Desensitization works both on intended effects and side effects (often). Re-sensitization occurs given time to readjust. **Physiological antagonism** is also known as **functional antagonism** – effects of histamine are functionally antagonised by adrenaline (anaphylaxis and epi-pen).

Acute response to agonists is good adaption results in down-regulation of receptors and desensitization → **chronic response** is bad.
Acute response to inverse agonists is detrimental as it inactivates receptors → receptors stabilise and sensitize → **chronically** unexpected benefits.