**TABLE OF CONTENTS:**

**Note to reader**: Drugs and drug classes are highlighted in green and bolded (e.g. **Aspirin**).

**LECTURE 2**: Drug Targets 25/07/17

- The **drug target** is the entity that the drug binds in order to have an effect.
  - Most drug targets are **proteins** (e.g. ion channels, transporters, enzymes, receptors).

| **Drug target**: | **Function**: | **How might a drug impact function?** |
|---|---|---|
| **Ion channel** | Allows the movement of ions into or out of cells. | A drug might modify or block the opening of the channel.<br>• Example: **Nifedipine** blocks L-type $Ca^{2+}$ channels. |
| **Carrier molecule / Transporter** | Allows movement across the membrane. | A drug might utilise or block carriers.<br>• Example: **Fluoxetine** blocks serotonin uptake channels. |
| **Enzymes** | Catalyses the breakdown / synthesis of molecules | A drug might inhibit enzymes (blocking catalytic activity).<br>• Example: **Neostigmine** inhibits acetylcholinesterase.<br>• Example: **Aspirin** inhibits cyclooxygenase.<br>A drug might need an enzyme to be activated. Drugs that are administered in an inactive form are **pro-drugs**.<br>• Example: **L-DOPA** is a pro-drug. It is converted into dopamine by DOPA decarboxylase. |
| **Receptor** | Transduces a signalling response. | A drug might activate or block a receptor.<br>• Example: **Morphine** activates opioid receptors.<br>• Example: **Naloxone** blocks opioid receptors. |

## Receptors as drug targets:

### Receptor nomenclature:

- Receptors are often named after the first known activator of the receptor.
  - **Cholinoceptors** are activated by acetylcholine.
  - **Adrenoceptors** are activated by noradrenaline and adrenaline.

### Receptor classes:

- Cholinoceptors can be divided into classes:
  1. **Muscarinic receptors** (which are named so, because the first known activator was muscarine).
  2. **Nicotinic receptors** (which are named so, because the first known activator was nicotine).
- Adrenoceptors can be divided into classes:
  1. **α-adrenoceptors**
  2. **β-adrenoceptors**

### Receptor subclasses:

- Receptors can be split into **subclasses** depending on their distribution and their physiological responses.
- **Tip**: You definitely need to know the location of receptors to do well in this subject.
- α-adrenoceptors can be split into subclasses:
  1. **$\alpha_1$-adrenoceptors**: Present on blood vessels.
  2. **$\alpha_2$-adrenoceptors**: Present on some presynaptic terminals.
- β-adrenoceptors can be split into subclasses:
  1. **$\beta_1$-adrenoceptors**: Present on the heart.
  2. **$\beta_2$-adrenoceptors**: Present on bronchial smooth muscle and some blood vessels

**LECTURE 3 & 4**: How do Drugs Interact with Receptors? 27/07/17, 31/07/17

- **Note**: In this subject, we tend to focus on the interactions between drugs and receptors.
- **Receptors** can bind **endogenous chemicals** (i.e. molecules that are normally present in the body) or **exogenous chemicals** (i.e. drugs).

## Agonists versus antagonists:

- **Agonists** are chemicals that bind the receptor and activate it.
- **Antagonists** are chemicals that bind the receptor, but do not activate it. If an agonist is present, then the binding of an antagonist prevents the receptor from binding the agonist (and being activated).

## Key pharmacological terms (affinity, efficacy, potency):

### Affinity:

- **Affinity** is the tendency of a ligand to bind to receptors, which depends on the ligand's molecular attraction to the receptor. All drugs should have affinity (because all drugs bind).

#### *How do we measure affinity?*

- The **dissociation constant** ($\mathbf{K_D}$) is the concentration of drug when 50% of receptors are bound.
  - $\mathbf{K_D}$ is a measure for affinity. The lower the $K_D$, the higher the affinity.

#### Where does the dissociation constant come from?

- The **Law of Mass Action** states that the reaction rate is proportional to the concentration of reactants.

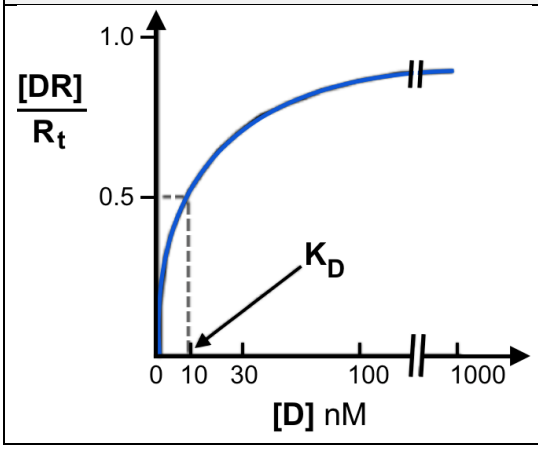
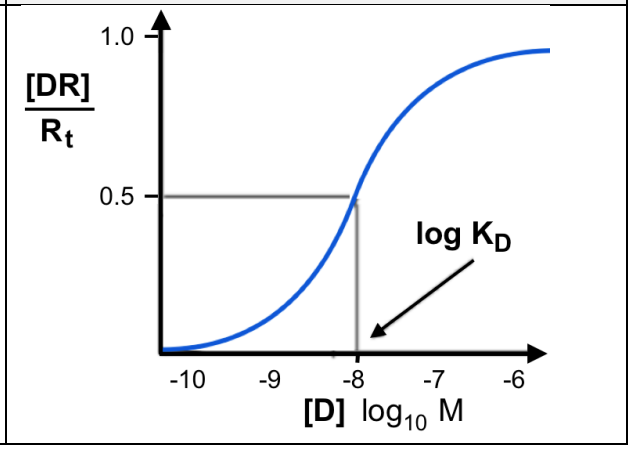
  $$[D] + [R] \rightleftharpoons [DR]$$ (where the **forward rate** is $k_1$ [D] [R] and **back rate** is $k_{-1}$ [DR])
  - The **fraction of bound receptors** ($[DR] / [R]_{total}$) is given by:

$$\frac{[DR]}{[R]_{total}} = \frac{[D]}{K_D + [D]}$$ where $\mathbf{K_D}$ is given by $\frac{k_{-1}}{k_1}$

    - If the fraction of bound receptors is 50%, then $K_D$ is equal to [D]. Thus, $K_d$ represents the drug concentration ([D]) in which 50% of receptors are bound. This is where $K_D$ comes from.

#### Concentration-receptor occupancy curve:

- $K_D$ can be read off the graph of the **concentration-receptor occupancy curve**, which plots the fraction of bound receptors (i.e. $[DR] / [R]_{total}$) against drug concentration (i.e. **[D]**).
- There are two ways to plot this curve: using a normal scale for [D] or using a log scale for [D].

| **Normal scale**: | **Log scale**: |
|---|---|
|  |  |





- ***Note***: The log scale is preferred due to its **sigmoidal shape**.

**LECTURE 20 & 21:** Drugs Acting in the Cardiovascular System 05/09/17, 07/09/17

## Cardiovascular system physiology:

### Components of mean arterial pressure (MAP):

- Equations: **MAP = CO × TPR** **CO = HR × SV**
- **Cardiac output** (CO) represents the litres of blood that is pumped per minute.
  - **Heart rate** (HR) is the number of heart beats per minute.
  - **Stroke volume** (SV) is the litres of blood pumped out with each heart beat.
- **Total peripheral resistance** (TPR) represents the overall constricted-ness of vessels in circulation.

### Preload and afterload:

- **Preload** refers to the filling pressure that results from venous inflow into the right atrium. *How much blood is returning to the heart from systemic circulation?*
  - If venous return is greater, then preload will be greater.
- **Afterload** refers to the resistance to arterial outflow coming out from the left ventricle. *How difficult is it to pump blood out of the left ventricle into systemic circulation?*
  - If total peripheral resistance is greater, then afterload will be greater.

### Regulation of blood pressure:

- **Baroreceptors** detect blood pressure. Baroreceptors are located in the **carotid sinus** and **aortic arch**.
- When blood pressure changes, baroreceptors adjust their firing rate to the **medulla** (the integration centre for the CVS). The medulla then adjusts the outflow of sympathetic and parasympathetic systems.

#### *Effects of sympathetic nervous system on blood pressure:*

- The sympathetic nervous system is more influential in the regulation of blood pressure.
- ↑ **HR**: By stimulating $\beta_1$ receptors on the nodal cells, which increases the activity of nodal cells.
- ↑ **SV**: By stimulating $\beta_1$ receptors on ventricular cells, which increases the force of contraction.
- ↑ **TPR**: By stimulating $\alpha_1$ receptors on vascular smooth muscle, which increases vasoconstriction.
  - These vessels include: Arterioles, veins.

#### *Effects of parasympathetic nervous system on blood pressure:*

- ↓ **HR**: By stimulating $M_2$-receptors on the nodal cells, which decreases the activity of nodal cells.

#### *Effects of the renin-angiotensin system:*

**angiotensinogen**
*secreted by liver*
↓ ***renin*** *secreted by kidney*
**angiontensin I**
↓ ***ACE*** *found in lungs*
**angiotensin II**

- **Angiotensin II** exerts the following effects:
  - Constricts the efferent arterioles in kidneys.
  - Increases $Na^+$ reabsorption in proximal convoluted tubules.
  - Stimulates the adrenal gland to release aldosterone.
  - Affects hypothalamus to increase sensation of thirst.
- **Aldosterone** exerts the following effects:
  - Increases $Na^+$ absorption in collecting duct.
- **Note**: Increasing $Na^+$ reabsorption increases blood volume, Hence, the renin-angiotensin system increases blood pressure.
- Sympathetic input:
  - Noradrenaline released from sympathetic neurons can stimulate $\beta_1$ receptors in the kidney, to cause release of **renin**.

**LECTURE 14 & 15:** Drug Discovery – Then and Now 22/08/17, 24/08/17

## Drug discovery in the past:

- There were four principles of drug discovery in the past: *observation* (*experience*), *serendipity*, *screening*, *synthetic chemistry*. These principles are still relevant for drug discovery, today.

### Observation (Experience):

- **Observation** (**experience**) refers to being aware of the things that are happening around you.
- Observations can occur within laboratories:
  - Example: Penicillin was discovered from the observation that *Staphylococcus* bacteria would not grow wherever the mould of *Penicillium notatum* grew.
- Observations can occur in the clinic by careful observations made by doctors:
  - Example: Orally-acting hypoglycaemic drugs (e.g. **Tolbutamide**) were discovered when doctors made the observation that **sulphonamide** lowered blood glucose.

### Serendipity:

- **Serendipity** describes the good fortune, lucky accidents that lead to discoveries that are even better.
  - Example: If Alexander Fleming's *Staphylococcus* culture wasn't contaminated with the mould of *Penicillium notatum*, he wouldn't have been able to make the discovery of penicillin.

### Screening:

- **Screening** involves collecting many compounds and searching through the compounds until you find the properties that you desire. Compounds can be collected from plants and microorganisms. Compounds are then purified and then assayed for activity.
  - Example: Pfizer (US drug company) collected 135,000 samples of soil. They screened millions of compounds and discovered **oxytetracycline** (a broad spectrum antibiotic).

### Synthetic chemistry:

- **Synthetic chemistry** involves using organic chemistry to produce:
  - A synthetic version of a natural product. Same structure as the natural product, but produced in the lab
  - A modified version of natural product. It tries to improve on nature.
  - An entirely new drug.
- Example: **Lysergic acid diethylamide** (LSD) was synthesised from lysergic acid.

## Drug discovery, now:

- The previous principles are still relevant today. However, now drugs are discovered in a more logical way. We use information about the structure of receptors and ligands, as well as biochemical pathways, to find an appropriate target to design a drug. This is **rational drug design**.

### Rational drug design:

- Approach to rational drug design: Choose disease → Choose target → Search for leads → Optimise leads → Preclinical development and toxicology → Clinical trials → Approval

#### *Choosing a disease:*

- When selecting a disease to design drugs for, we consider economic and scientific issues:
  - To make projects sustainable, drug companies need to make a profit so that they can continue making drugs to treat other conditions. Thus, diseases with many patients make good diseases to treat first.

**LECTURE 24**: Drugs of Dependence 14/09/17

- Increasing *dopamine* neurotransmission in the brain, is common to all drugs of abuse and dependence

## Dependence vs. abuse:

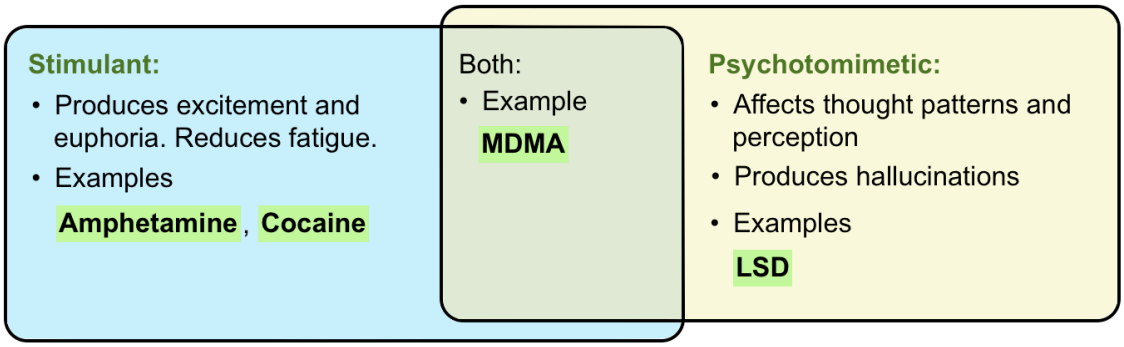
- **Drug dependence**: Is when drug taking becomes compulsive and takes precedence over other needs.
- **Drug abuse**: Refers to the use of illicit substances or the illicit use of legal substances (e.g. using without a prescription). This has clinically significant adverse consequences.

## Stimulants vs. depressants:

- Drugs can be **stimulants** or **depressants** of the central nervous system (CNS).

| **Legal**: | **Illegal**: |
|---|---|
| • **Ethanol**: Depressant<br>- Depresses the limbic system, anxiety centres and stress centres. | • **Cocaine**: Stimulant<br>• **Amphetamine**: Stimulant<br>• **LSD**: Stimulant<br>• **MDMA** (known as ecstasy): Stimulant<br>• **Cannabis**: Depressant (only particular chemicals from cannabis are legal) |

### Stimulants:




## Psychological vs. physical dependence:

- In **psychological dependence** (addiction), there is a psychological drive that requires periodic or continuous administration of the drug to avoid discomfort or produce pleasure.
- In **physical dependence**, there is a withdrawal syndrome consisting of physical symptoms. These symptoms appear when drug use is stopped abruptly. It is accompanied by **tolerance** (the need to take a higher dose of drug in order to have the same effect).

### Reward pathways:

- **Mesolimbic-dopaminergic pathway**: Drugs of dependence increase dopamine in nucleus accumbens. Dopaminergic neurons project from the ventral tegmental area (VTA) to the nucleus accumbens. The nucleus accumbens is an area strongly associated with reward.
  - **Note**: GABA is the main inhibitory neurotransmitter of the brain and can inhibit dopaminergic neurons. Some drugs inhibit GABA, which increases dopaminergic transmission.
  - The VTA receives input from the amygdala (involved in stress) and locus ceruleus (involved in arousal)
    - If a person is aroused when they take the drug, this can lead to higher incidence of addition.
    - If a person is stress when they take the drug, this can prompt a relapse.

**MID-SEMESTER TEST (MST)**: 2017 Semester 2

## About the MST:

- In 2017, the MST ran for 40 minutes (there was no assigned reading time), had 40 questions and 40 marks. Seat numbers for the test were released about a week or two prior to the test. Lectures that were examined included *Lecture 1* to *Lecture 18*.
- **Note**: Lectures are examinable. Content from tutorials and questions from SDLs are examinable. (Content from practicals is only examinable if all of the cohort has completed their practical before the MST).

## Preparing for the MST:

- Here's a checklist to help you gain an idea of what you need to know for this test:

| From: | Content: | |
|---|---|---|
| Lecture 1 | • Understand the principles of pharmacology. Be able to apply them! | |
| | • Understand the difference between pharmacodynamics and pharmacokinetics. | |
| Lecture 2 | • Understand the various drug targets: ion channels, transporters, enzymes and receptors. Know examples of drugs for each drug target. | |
| | • Understand the various receptor families: including location, structure, time frame, examples and their mechanisms. | |
| | • Understand that G-protein coupled receptors can be coupled to different G-proteins. Understand the mechanisms of each G-protein type. | |
| Lecture 3 & 4 | • Understand the difference between an agonist and an antagonist. | |
| | • Understand affinity, efficacy and potency: including how we measure affinity, how we measure potency, and the difference between full and partial agonists. | |
| | • Understand different forms of anatgonism: competitive antagonism (including the difference between surmountable and insurmountable), non-competitive antagonism (including allosteric modulation, pathway inhibition, functional antagonism). | |
| | • Understand the use of antagonists to determine whether two drugs act at the same or different receptor. | |
| Lecture 5 | • Understand the difference between the somatic and autonomic nervous system. Basically, memorise the diagram on *p. 9* (or an equivalent diagram). | |
| | • Understand the fibre length for preganglionic and postganglionic fibres in parasympathetic versus sympathetic nervous systems. | |
| | • Understand chemical transmission at the synapse. | |
| Lecture 6 | • Know the endogenous agonists of adrenoceptors, and how they are synthesised. | |
| | • Understand the tissues / organs that have adrenoceptors (including the subclass, e.g. heart contains $\beta_1$, and including the physiological response upon receptor activation). | |
| | • Understand how noradrenaline is released in the synapse (including exocytotic release and non-exocytotic leak). | |
| | • Understand how noradrenaline is inactivated in the synapse (including reuptake and metabolism by MAO and COMT) | |
| | • Know drugs that affect the release of noradrenaline (including IAS drugs) | |
| | • Know drugs that affect the inactivation of noradrenaline (including cocaine and MAO inhibitors). | |
| | • Know the drugs that are agonists of adrenoceptors (including what subclass each drug is an agonist of). | |
| | • Know the drugs that are antagonists of adrenoceptors (including what subclass each drug is an antagonist of). | |
| | • Understand what kind of G-protein each adrenoceptor is coupled to. | |