Lecture 16 – Drugs and poisons

As a matter of public interest, governments have become heavily involved in the control, legislation, packaging and production of drugs (or poisons). There is references to controlling substances from the 14th century. Today, we control poisons to prevent; poisoning, suicide, crime, dependence, abuse, microbial resistance, sensitisation etc.

Victorian History

The first attempt to establish a poisons act in Victoria was 1857 (failed) and 1876 (passed the *Sale and Use of Poisons At 1876).* The first comprehensive Act from the Victorian Parliament to restrict the availability of certain drugs was the *Drug, Poisons and Controlled Substances Act* of 1981. Very rudimentary compared to today's standards. From then on, drugs control has been bureaucratic, always detailed, data intensive and subject to frequent amendments

Scheduling Drugs

Today, pharmacies have to abide by the standard for the uniform scheduling of medicines and poisons (SUSMP). This is a list of drugs and poisons divided into nine categories called "schedules". *Opiates come from the poppy, opioids is all of those plus synthetic products which mimic the effect. **Medicinal cannabis has caused huge changes in state and federal law, there is a new act called the *Access to Medicinal Cannabis Act 2016,* which has occurred extremely quickly (in comparison to S8 electronic systems which Pharmacists have been asking for continuously).

Schedule	Description of schedule	Example drug
Schedule 2	For therapeutic use, labelled pharmacy medicine	Simple analgesics, cough and cold medicines, iron tablets e.g. nurofen (ibuprofen) of packs < 25 tablets
Schedule 3	For therapeutic use, supplied by pharmacist only so long as he/she has determined that the patient has therapeutic use for the product	Ventolin (salbutamol), nurofen plus (ibuprofen 200mg with codeine phosphate 12.8mg), panadeine extra (15mg codeine phosphate) and pseudoephedrine e.g. sudafed
Schedule 4	Prescription only or animal remedy only. Possession without authority is illegal	Diaformin (metformin for diabetes), antibiotics, blood pressure drugs, benzodiazepenes
Schedule 5	Hazardous household substances labelled CAUTION but available anywhere	Liquid hydrocarbons, weak mineral acids, some garden chemicals
Schedule 6	More toxic substances for agricultural or industrial use. Available everywhere. POISON	Stronger acids and alkalis, eucalyptus oil
Schedule 7	Very dangerous poisons with specialised non-therapeutic uses. Labelled dangerous poison	Organophosphorus compounds, cyanides, strychnine, arsenic
Schedule 8	Drugs of addiction. Labelled controlled drug (prescription only) so possession without authority is illegal. Detailed records kept.	Morphine, endone (oxycodone), alprazolam, amphetamine, flunitrazepam, pethidine
Schedule 9	Prohibited substances, high likelihood of abuse. Permitted for research but needs approval	Heroine, cannabis, hallucinogens

Controversial continuum

There are problems with whether 'foods' such as Ribena (vitamin C substances), Sustagen gold (protein supplements) and staminade could be classified as foods or medicines. This was controversial as the companies didn't want to be classified as medicines as they would have to be regulated and taxed. Same problem with cosmetics vs drugs.

Therapeutic Goods Act 1989

Over 500 pages which seeks to maintain a national system for controlling the "quality, safety, efficacy and timely availability of therapeutic goods". It sets standards (including licenses) for pharmaceuticals e.g. recall procedures for faulty products. A **therapeutic good** is defined as anything you take for medicinal use. Once defined as a therapeutic good, it will be evaluated and manufacturers have to be licensed by the TGA (however, the final product is *not* evaluated by the TGA).

- **Quality –** medicines reach certain standards including good housekeeping
- **Safety –** balancing risks versus benefits including limitations on use, dose, frequency and duration
- **Efficacy –** is there a reasonable expectation that the medicine will perform as claimed? Individual product evaluation and registration as well as restrictions on labelling and hyperbolic advertising

Main failure of the system is the "AustL" system which means the product is safe and quality, however efficacy is not tested and often questionable in comparison to scientific data e.g. Fat Blaster Max

Lecture 17 - Asthma Therapeutics

Estimated that 10% of the population is directly affected by asthma. It is an allergic response ultimately leading to **bronchospasm mucous vascular leak** and obstruction of the lungs. Interestingly, your lung health / capacity will peak at the age of 25, so your conditioned health up to then affects your lungs for the rest of your life.

Asthma Pathogenesis

A disease which has polygenic influences, with even more **epigenetic** influences (environment + genes). This induction event takes several weeks but re-introduction will result in a response within seconds / minutes.\

1. Antigen-presenting cell recognises an 'allergen' in the environment and T lymphocytes proliferate
2. T-lymphocytes recruits pro-inflammatory cytokines. The Th2 lymphocyte in particular makes an extreme amount of IL-3, IL-4 and IL-5. (these act as recruiters)
3. Pro-inflammatory cytokines recruits interleukins which recruit B lymphocytes (IL-4; produce IgE) , mast cells (IL-3; increases B-lymphocyte longevity) and eosinophil (IL-5). *IgE is a cytotropic antibody which means it has high affinity for the mast cell to enable the mast cell to release histamine and make leukotrienes to destroy the allergen. As a result of the leukotrienes and other mediators...
4. Inflammatory response of the respiratory system, resulting in ultimate bronchospasm mucous vascular leak

Inflammatory mediators

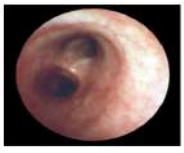
Loss of integrity of the epithelium in the lungs (caused desquamation) increases the disruption of inflammation of asthma. A good production of mucous and functioning cilia for expectorating is also important for protecting the airways.

Inflammatory mediators	Molecule recruited	Function of the molecule
Mast cells	Histamine	Blocking histamine receptors has no clinical benefit. Therefore, the histamine contribution overall isn't significant enough to make a difference
Eosinophils	Cysteinyl-leukotrienes	More potent than histamine. Persistence of the contraction that cysteinyl-leukotrienes cause is the key factor of their destruction i.e. slow spasm of the muscle causing muscle narrowing and shortening
Macrophages	Prostaglandins	Net influence still uncertain
T lymphocytes	Interleukins	Set the scene for the next day's reaction, elevated response maintains a state of readiness for the next inflammatory response (like keeping the engine on)
Nerves	Neurokinins	Net influence still uncertain

Defining asthma

Three main symptoms determine whether a person has asthma;

1. **Airway obstruction** – bronchial blood vessels become leaky and dilated. Mucous cells and glands are activated. Results in mucosal oedema which narrows the lumen (increasing its resistance to airflow)
2. **Chronic eosinophilic airway inflammation**
3. **Increased airway responsiveness** – airways narrow too easily and too much



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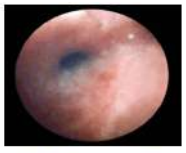


10 minutes after allergen challenge

Airway smooth muscle

Contracting airways – M3, H1 and CysLT1 receptors (parasympathetic response)

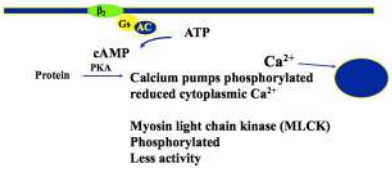
Relaxing airways – opening the airways is a sympathetic response i.e. beta 2 adrenoceptors

#1 Relievers (SABA)

(SABA – Short acting beta 2-adrenoceptor agonist) – controlling the **smooth muscle constriction**

e.g. **Salbutamol / Terbutaline –** acute bronchodilator therapy using activation of beta 2 – adrenoceptors. Rapid onset of action within 2-5 minutes (half time of the measurable physiological dilation that the drug causes is 2-4 hours). Possible adverse effects includes tremors or tachycardia if beta1-receptors are also activated

*Recall, using an agonist of the beta 2 – adrenoceptor relaxes the airways because increased cAMP and PKA results in calcium pumps *reducing* ECF Ca2+ therefore, there is less activation of MLCK. If there is less shortening of the muscle then the airways dilate!



#2 Controllers (LABA)

(LABA – Long acting beta 2-adrenoceptor agonists) – controlling the **smooth muscle constriction**

e.g. **Salmeterol / formoterol -** exactly the same mechanism of action but have a longer persistence. Relaxes the airway all the time so that you are preventing constriction throughout the day, relieving symptoms to those with severe asthma. Their use will combine with anti-inflammatories as asthma at this stage is highly severe and needs the added help.

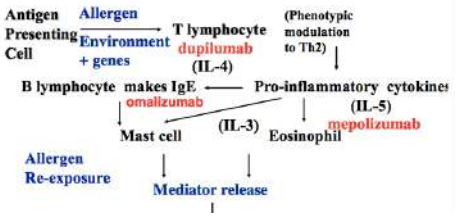
#3 Preventers (cysteinyl-leukotriene receptor antagonists)
Orally active e.g. **Zafirlukast, Montelukast.** – controlling the **smooth muscle constriction**
Less effective as it is subject to first pass hepatic metabolism but it does result in modest bronchodilation by blocking the cysteinyl leukotriene receptors and causing less muscle spasm of the airways. As the receptor target is more specific, their tends to be fewer side effects.

#4 Glucocorticoids
e.g. **Budesonide, fluticasone propionate, prednisolone (oral)**
Binds to the cytosolic receptor which represses and activates other genes – controlling the **inflammation**
In the DNA, the drug alters the production of genes to suppress production of inflammatory cytokines and inflammatory enzymes. It can also **induce annexin synthesis** to reduce phospholipase A2 activity. The first effect is seen within hour to days but can take weeks to months to reach their maximum therapeutic effect.

The overall impact is to decrease the number and activity of the inflammatory mediators. Can be used by inhalation or taken orally but inhalation causes the most damaging effects, including growth suppression. Can be used short-term to bring asthma back under control or can be used more permanently for severe asthma patients.

Lecture 18 – Immunopharmacology
Referring to a chemically and functionally diverse set of drugs that influence the immune system either beneficially or detrimentally. Products can be; natural, low molecular weight, cytokines and/or monoclonal antibodies. Immunopharmacology is most relevant for allergic diseases, autoimmune diseases, graft rejection and cancer.

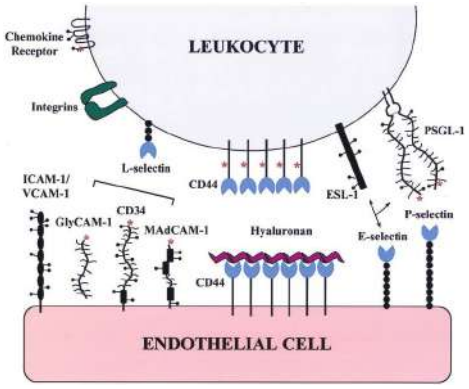
Monoclonal Targets
1. **Dupilumab** - neutralises interleukin 4 in a person who has already been sensitised i.e. diminish the impact of the second immune response.
2. **Omalizumab** - Prevents IgE being produced from B lymphocytes.
3. **Mepolizumab** - Neutralises interleukin 5 to diminish the frequency and strength of the immune/allergy response in a subject.



Allergic Diseases
Atopy – a condition / tendency to produce larger amounts of IgE. *Recall that IgE binds to mast cells to encourage cross-linking (kinases activated through a calcium release after binding to Fc receptor) and mast cell activation. Mast cells then release histamine and bioactive lipids like prostaglandins and leukotrienes. The result is; smooth muscle constriction, oedema, mucous secretion and infiltration by leukocytes.

To treat allergic diseases we can avoid allergens or treat using pharmacology by;
1. Decreasing **mast cell mediator** release – disodium cromoglycate
2. Decreasing **actions** of **mast cell products –** useful in nasal and skin allergies but not in asthmatics e.g. antihistmaine
3. **Preventing IgE from binding** to mast cells so as not to activate the mast cells e.g. omaluzimab

Omalizumab
A humanised antibody which can be administered subcutaneously. This monoclonal antibody binds to the Fc receptor, therefore, competing with the IgE on the mast cell and preventing it from binding. If we reduce IgE activation then we can reduce asthmatic and allergic rhinitis symptoms. More effective with patients suffering from a higher IgE serum level.
Trafficking leukocytes and lymphocytes
They traffic from the bone marrow, through the circulation, then into the tissues. This assists in protecting all of our surfaces exposed from the outside environment from infection / injury in the meantime i.e. as it is travelling. We need constant trafficking (called **rolling)** to provide this systemic protection.



1. Travelling mast cell mediators activate **selectins** on the cell surface – they have corresponding ligands on the leukocytes to you get a sugar-sugar interaction. This means the inflamed tissue can grab up the leukocytes to allow the immune cell to engage its immune response and start a signalling pathway. These selectins are also helped by **cellular adhesion molecules** which stop the leukocytes rolling by using stationary binding. CAMs are a type of **integrin.**
2. This process can be blocked therapeutically e.g. **natalizumab** which target ligands of CAMs to reduce leukocyte entry into the CNS to prevent the immune response of the body attacking itself. This medicine is particularly

helpful in multiple sclerosis where the leukocytes are unmyelinating axons in the CNS. However, there is an adverse effect as it increases the risk of viral infections, which can be fatal.

Autoimmune Diseases

Attacks of over-present or over-active T cells, macrophages and neutrophils. This results in deposition of more connective tissue and blood vessels but decreases the bone mass. Therefore, you get swelling, reddening and pain. Interestingly, prostaglandins contribute to most of these effects but they *decrease* leukocyte and endothelial cell activation and *reduce* cytokine release and they increase bone reabsorption.

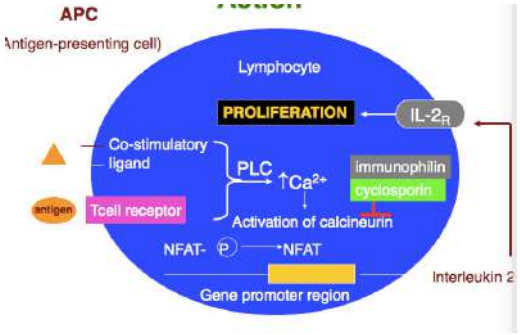
To treat using NSAIDS, you can improve blood flow and level of pain but long term you affect; bone reabsorption. Therefore, you can't influence the disease progression and you can actually aid the long-term effects of a disease e.g. bone loss in rheumatoid arthritis. Another example is unselective NSAIDS can induce stomach ulcers by reducing mucus secretions in the stomach lining.

Graft Rejection

We want to suppress the immune system as it will be reacting *against* the presence of a foreign tissue. In patients with grafts, we see T and B lymphocytes increases dramatically. Therefore, **immunosuppression** treatment is required for **life**. So the toxicity of these drugs causes significant long-term effects such as increased risk of cancer and infection.

Immunosuppression treatment

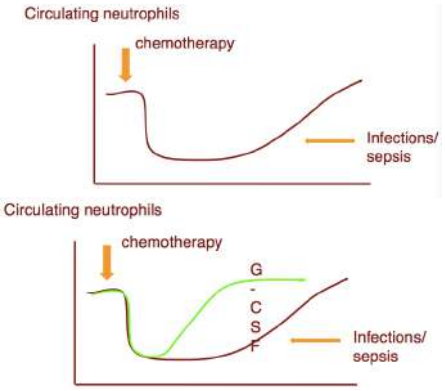
Cyclosporin is a natural product derived from fungus. It has a more selective product. *Recall when an antigen binds to a T cell then it increases action of phospholipase C which increases calcium, activates calcineurin, (a phosphatase) activates Nuclear Factor of Activated T-cells NFAT (by removing a phosphate) and eventually creates **interleukin 2.** Interleukin 2 can then cause proliferation of many lymphocytes.



What the cyclosporin does is block the activation of the calcineurin by activating a natural inhibitor of calcineurin called **immunophilin** so that NFAT isn't activated and interleukin 2 isn't produced.

Cancer Chemotherapy

e.g. **Azathioprine** is a treatment of -selective cytotoxics which **suppresses cell division.** Therefore, it is a relatively non-selective anti-cancer agent. It stops cell proliferation and encourages cell death but unfortunately also affects the bone marrow by suppressing its activity. If you suppress the bone marrow, then you suppress the amount of lymphocytes and neutrophils that you can create, so you increase your risk of infection.

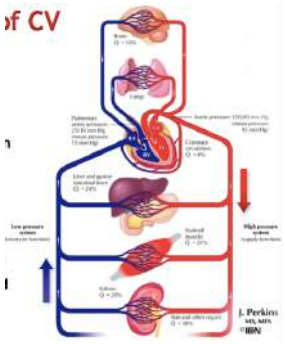


To target this **neutropaenia** (not enough circulating neutrophils) we use recombinant **granulocyte colony stimulating factor (G-CSF)** which is a stimulator of the colonies of precursors for neutrophils, therefore increases proliferation and number/action of neutrophils. The result is a decrease in neuropenic fever and infection rates in chemotherapy patients.

Lecture 19 – Drugs in the Cardiovascular System

Basics of the Cardiovascular system

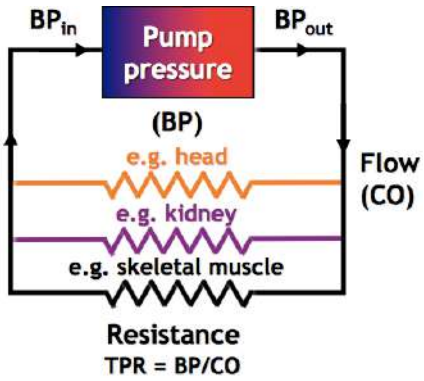
The heart propels blood to the lungs via the right ventricle then onto the systemic circulation via the left ventricle. Thus, the left ventricle is the 'high pressure' side with a greater percentage of muscle. In terms of the systemic circulation, you have the arteries and arterioles (**distributing tubes**) and your veins and venules (**collecting tubes**) which are considered to be your blood reservoir as 70% of blood volume is contained in this low pressure side.



Finally, you have the capillaries which are purely endothelial cells so are not a site of blood pressure control. They allow for rapid exchange between tissues and vascular channels.

Component of blood pressure (BP)

BP = CO X TPR where CO – HR x SV. Total peripheral resistance is the easiest to be manipulated as we have humoral, sympathetic and local regulation of this condition. Note that the kidneys will also affect blood pressure long-term as it regulates intravascular fluid volume (changing the Starling forces and therefore, affecting the MAP).



- **Control of heart rate -** Heart rate is affected by sympathetic activity as sympathetic releases noradrenaline (and adrenaline from the adrenal gland) which both work on **beta 1 adrenoceptors** so increase heart rate at the SA node. On the other hand, parasympathetic activity will release ACh which works on **muscarinic 2 receptors** to stimulate the SA node and decrease the heart rate

- **Control of stroke volume –** is only affected by the sympathetic nervous system through noradrenaline and adrenaline acting on the **beta 1 adrenoceptors** on the cardiac muscle to increase the force and contractility of the heart

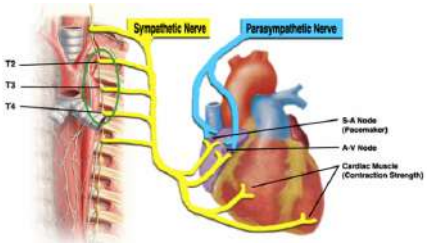
- **Control of cardiac output –** if you increase the preload (fill the right side of the heart more and increase pressure) then you will result in a greater arterial outflow.

Dangers of hypertension

Often called the silent disease, moderate to severe hypertension can go undetected but cause kidney disease, ischaemic stroke, left ventricular hypertrophy and vision damage which leads to stroke, artery disease, heart failure and/or renal insufficiency over time. Factors which contribute to hypertension includes age, diets high in Na^+, genetics, obesity and even renal or endocrine disorders.

Treatment is not only to lower the blood pressure but to prevent **cardiovascular sequelae.**

1. **First choice therapy –** lifestyle modifications including an increase in physical activity, no alcohol, weight loss, quitting habits such as smoking, and eating a low sodium diet
2. **Pharmacological therapy –** we tend to prefer to lower blood pressure by decreasing the **sympathetic** effects on the heart i.e. affecting cardiac output by manipulating the adrenoceptors. (Parasympathetic nerves *only* affect the nodes, not the muscle as well, so it's more effective to target the sympathetic nervous system).



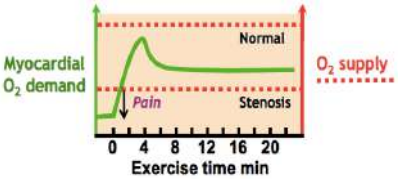
Recall that activation of beta-1 adrenoceptors cause a positive **ionotropic** effect, which increases the force of contraction, and also causes a positive **chronotropic** effect which increases the rate of contraction. As such, we found beta 1 adrenoceptor antagonists which antagonise **cardiac** beta receptors to decrease HR at the SA node and decrease SV at the cardiac muscle. *Side note: it also inhibits renin secretion of the kidney which decreases its volume and tone

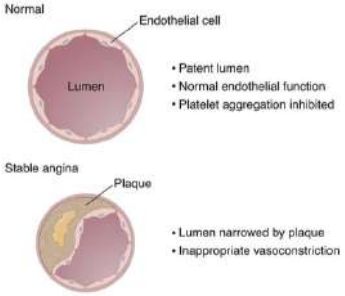
Beta-1 adrenoceptor antagonists

Older beta blockers are non-selective which means they affect beta 1 and beta 2 receptors e.g. propranolol. Unfortunately, these drugs are lipophilic which means they cross easily into the brain. On the other hand, beta-1 selective antagonists are cardio selective and are **hydrophilic. Side effects** of the drugs will are mostly attributed to beta 2 receptor inhibition, causing symptoms such as fatigue, insomnia (if lipid soluble drug), cardiac depression, bronchoconstriction and cold extremities

Stable Angina pectoris

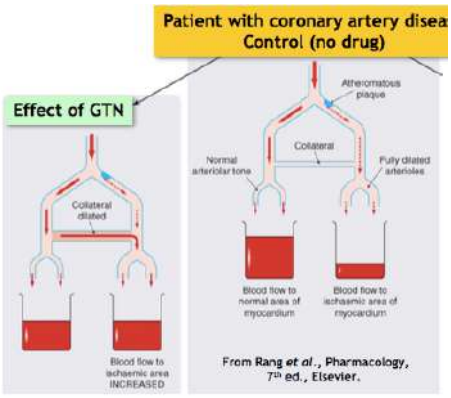
Clinical manifestation of chronic coronary artery disease which causes a pain/crushing sensation in the chest which is caused by reversible myocardial ischaemia. If the heart is working too hard, e.g. could be because of exercise or hypertension, then the myocardial oxygen demand increases. If the demand increases above the oxygen supply possible, then you get the pain of angina. **Stenosis** is the condition of a limited oxygen supply due to artherosclerotic disease, often a plaque or narrowing of some sort.





Pathophysiology of angina syndromes

Someone with angina will have stenosis due to narrowing of lumen by plaque or inappropriate vasoconstriction. This therefore decreases the ability of blood to flow to tissues so will cause pain when exerting above a certain oxygen demand level. Stenotic lesions can be eccentric (plaque/narrowing on one side of the lumen) or concentric (rigid wall or narrowing/plaque all around the lumen). Eccentric lesion is more dangerous than concentric because the other wall can contract normally so any normally constrictive stimulus can completely obliterate the lumen and cause actual spasm in the stenosed section.



Treatment with nitrates

For example **glyceryl trinitrate (GTN)** which is a **pro-drug** i.e. converting into nitric oxide in the blood. GTN can relieve angina in minutes sublingually (under the tongue) by decreasing cardiac oxygen consumption (reduced preload and afterload) and by dilating collateral vessels to help redistribute blood flow to the ischaemic area. The effects are;

1. NO stimulates guanylate cyclase
2. cGMP levels increase
3. Vasodilation in the veins
4. Decrease in preload on the heart
5. Decrease in myocardial oxygen demand
6. TPR of the arterioles also decreases due to the vasodilation. By dilating coronary collateral vessels (connect between major coronary arteries) you can get relief of vasospasm and increase the perfusion of ischaemic myocardium

Side Effects of GTNs

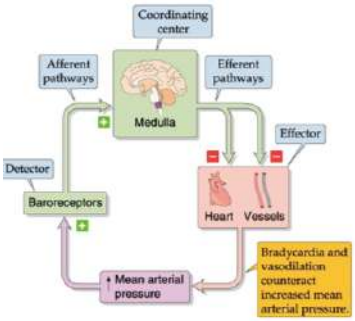
As well as *coronary* vasodilatation, you can also get **peripheral** vasodilatation. Therefore, you get rapid decrease in blood pressure and reflexive tachycardia or increase in vascular tone via the Baro reflex. This means that the action of the nitrates is entirely counteracted by its own side effect! This is why we see side effects including;

1. **Venodilatation** – orthostatic hypotension due to blood pooling in lower extremities from venodilatation
2. **Flush in face and neck –** due to dilatation of arterioles
3. **Headache –** dilatation of meningeal arterial vessels

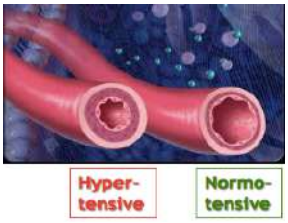
Lecture 20 – Blood Vessel Effectors

Blood Pressure

Blood pressure is under reflex control of the Baro reflex, using the medullary cardiovascular control centre as the integrating centre. The baroreceptors are in the carotid artery and aortic arch, and they are classified as "stretch" receptors.



Resistance to blood flow is described by **Poiseuille's Law** which describes resistance as being proportional to $1/r^4$. Using this law, we can show how any small change in the radius of the arteriole will have a dramatic effect on the resistance to blood flow.



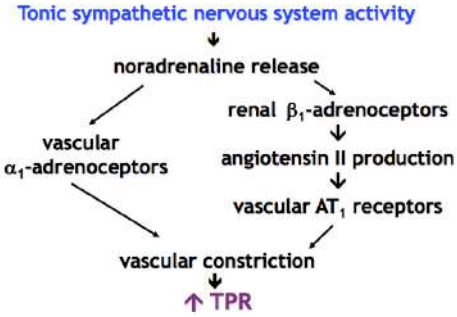
Hypertension

Long-term high blood-pressure results in structural changes in the blood vessels including; **hypertrophy** of smooth muscle and **decreased** vessel lumen. This is a protective mechanism to prevent the vessels from 'bursting', also known as **inward remodelling.** Ironically, the protection mechanism is contributing to the problem. Keeping the blood pressure regular can help return the vessels to a normo-tensive level.

Controlling Arteriolar diameter

In general, diameter is controlled by sympathetic nerves (with very few exceptions being controlled by the parasympathetic system). Therefore, the major therapeutic target for hypertension involves decreasing the sympathetic effect on arteries to decrease TPR. There are other factors affecting arteriolar diameter including;

- Hormones – angiotensin II, vasopressin
- Catecholamines – noradrenaline and adrenaline
- Pressure – a passive factor
- Local factors – endothelin-1, PGI2, NO



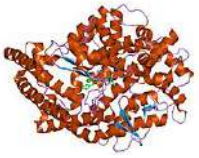
Basal Vascular Tone

Adrenaline acts at alpha-1 for the blood vessels and beta-1 for the heart and kidney. Interestingly, stimulating the beta-1 adrenoceptors on the *kidney* results in angiotensin II production which will also cause vascular constriction.

Alpha-1 Adrenoceptor Antagonists

Major side effects so used for moderate to severe hypertension in combination with other drugs. It causes arterial and venous dilatation. Anything ending in "zosin" means alpha-1 selective antagonist, for example prazosin.

These antagonists inhibit the vascular alpha-1 adrenoceptors, which decreases noradrenaline-mediated vasoconstriction to decrease TPR and BP. Side effects is postural hypotension (especially in elderly patients with weaker veins) which causes initial reflex tachycardia (especially potent in the first diose). Can also cause nasal congestion but the bigger problem is the postural hypotension because you don't want them standing up, feeling dizzy because the fall in blood pressure can't be fixed with an increase TPR so the elderly risks falling and breaking a bone.



Renin-angiotensin-aldosterone axis

Angiotensin is a peptide hormone released from the **kidney.** It starts as **angiotensinogen** → angiotensin I + angiotensin-converting enzyme (ACE) → **angiotensin II.** Angiotensin II is the big guns, and has four three effects;

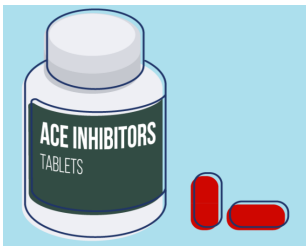
1. **Aldosterone –** increased release from the adrenal cortex which helps retain sodium to increases blood volume
2. **Systemic arterioles –** causing vasoconstriction which increases TPR
3. **Hypothalamus –** increases thirst

Angiotensin II

AT1 receptors are found in vascular smooth muscle, myocardial tissue, adrenal cortex, kidney and brain. Most known actions of angiotensin is by mediating the **angiotensin I receptors.** Fun fact, angiotensin II also contributes to hypertrophy of vascular smooth muscle and myocardium.

ACE inhibitors

Inhibiting the angiotensin-converting-enzyme which stops angiotensin I being converted to angiotensin II. With less angiotensin II in circulation you get less vasoconstriction, less aldosterone secretion from the kidney → less Na+/H2O retention → less blood volume, therefore less preload → blood pressure decreases. *__Fun fact:__ by preventing angiotensin I stimulation long-term, we can also prevent arterial wall remodelling to inhibit or decrease hypertrophy of muscle.



ACE examples

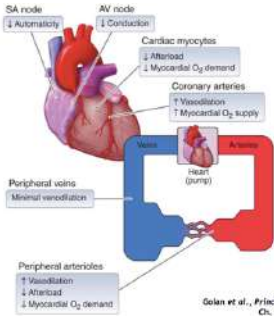
Suffix of "pril" e.g. captopril and enalapril. In the first dose, you can see side effects of hypotension (affecting the veins) and hyperkalaemia (too much K+ due to the effect of decreased aldosterone on the kidney). There is also often a persistent dry cough (due to ACE inhibiting the inactivation of bradykinin).

AT1 Receptor antagonists

e.g. **Losartan.** Directly inhibiting the angiotensin II from binding on the kidney, myocardium or vessels. You get the same effects of hypotension, hyperkalaemia and renal problems but you don't get the dry cough because you're not affecting bradykinin. You have the added advantage of preventing the cardiovascular remodelling as well.

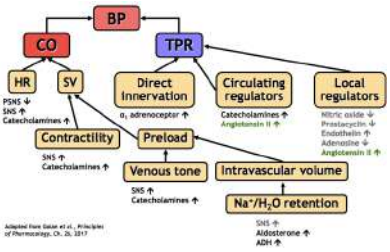
L-type Calcium Channel Antagonists

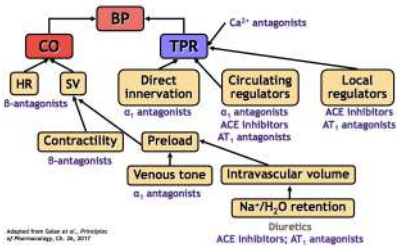
We now know that calcium influx through the L-type channel is important for vascular tone and cardiac contractility. Note L-type stood for "long-lasting". Vascular smooth muscle contraction needs free, intracellular [Ca^{2+}], therefore by inhibiting the calcium influx you can decrease vascular contractile tone and decrease TPR to decrease the blood pressure. There are three classes of calcium channel blockers;



1. **Dihydropyridines (DHPs) –** nifedipine, felodipind, amlodipine. The most important class to remember for this course. Vascular selective and adverse effects are a result of decreasing the blood pressure i.e. reflex tachycardia, palpitations, nausea, flushing, headaches
2. **Benzothiazepines –** diltiazem
3. **Phenylalkylamines –** verapamil

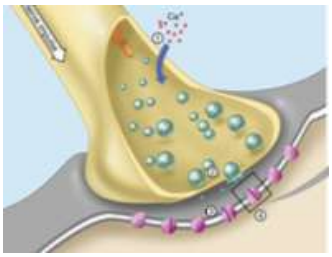
All of these antagonists causes the relaxation of **arterial** smooth muscle but luckily have little effect on veins so we don't get the reduced preload which causes hypotension. There is also little effect on skeletal muscle because L-type calcium channels aren't in muscle.





Lecture 21 – Introduction to CNS Pharmacology

**Nootropics - drugs which make us smarter



Synapses in the CNS

Synapses in the CNS are different to synapses at the NMJ. Neurotransmitter release is still calcium dependent, but differences include;

- Action potential causes a small change in membrane potential in neuron (not muscle)
- Several neurotransmitters stored and released, and they can be excitatory or inhibitory
- Whether a NT is excitatory/inhibitory is dependent on the **receptor** sub-class it binds. This is why serotonin can be excitatory and inhibitory.

Neurotransmitters released in the CNS

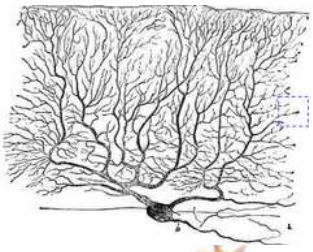
Too many to name here but there are five main categories;

1. **Acetylcholine** – muscarinic and nicotinic transmitters
2. **Amines** – such as noradrenaline, dopamine, serotonin, histamine – all have specific receptors
3. **Amino acids** – GABA is the main inhibitory and glutamate is the main excitatory
4. **Peptides** – LH, insulin, angiotensin, endorphin, oxytocin, glucagon
5. **Novel** – nitric oxide, ATP, carbon monoxide. Nature is good at hijacking biological processes to affect changes

Developing Drugs with CNS considerations

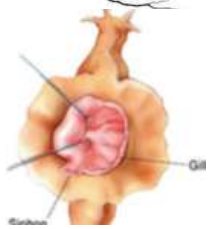
Drugs which cross the blood-brain barrier have serious CNS side effects, therefore, are less likely to exist to markets. Drugs go into the clinic with drug-company backing to make money, curing disease is the positive by-product. Dopamine and serotonin are notoriously difficult as there are many different receptors that are difficult to be selective for. This is one reason why it is so difficult to treat diseases such as depression.

Formation of memory



The biggest driver for memory-improving drug development comes from the military.

- **Short-term memory –** involves changing the effectiveness of a synapse. More neurotransmitter is released from a synapse following *repeated* stimulus
- **Long-term memory –** instead of evoking more neurotransmitter, long term memory evokes actual changes in your neuronal architecture. This is possible because of neuro-plasticity where you get the formation of dendritic spines, which is the beginning of the formation of long term memory. The process involves protein synthesis, involving phosphorylation of kinases which activates it to begin structural changes to the neurons.



Invertebrate models are often chosen as they have experimental advantages which help us to investigate and test drugs e.g. *Aplysia* invertebrates have large neurons, identifiable neurons and circuits and simple genetics.

Action of medicines

1. **Atomoxetine (Strattera)** – selective noradrenaline reuptake inhibitor for ADHD
2. **Mephylphenidate (Ritalin)** - dopamine and noradrenaline reuptake inhibitors. It is a stimulant and is a therapeutic drug for ADHD patients. We are giving a stimulant to ADHD patients as dopamine increase in areas of the brain which allow for concentration. Increases brain glucose metabolism and fine-tunes neurons in prefrontal cortex.

Lecture 22 – Drugs for Obesity

Definition of Obesity

Based on the BMI index (weight / height^2) where obese is >30 and morbidly obese is >40. According to the Australian Bureau of Statstics 2011-2012, 63% of Australian adults were overweight or obese. The complications with obesity is an increase in health risk for diseases including; diabetes, sleep apnoea, osteoarthritis, cancer, fatty liver disease and coronary heart disease.

Control of Appetite

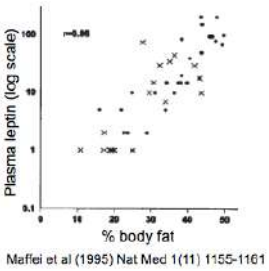
In general, the hypothalamus is where most of our energy/weight processes occur

- **Adiposity signals** – long term signals - adipose tissue releases **leptin** and the pancreas releases **insulin** which is sent to the hypothalamus to tell you that you are full e.g. when leptin levels are high, that turns off appetite
- **Satiety signals** – short term signals - sympathetic nervous input and hormones from the liver and stomach (sent to the **medulla)** which gives us an indication of our satiety.. Regulatory peptides are summarised below;

We can't create a drug to 'treat' obesity because of the complexity and number of hormones which defends our body weight regulatory system. There is 'redundancy' in our physiology which prevents starvation when one hormone isn't working or being produced as intended.

Leptin

A peripheral, anorexigenic hormone (decreases appetite and feeding). Leptin is secreted predominantly from fat cells. It crosses the blood-brain barrier (via a saturable process because it is a large protein so it needs transporters to get into the brain). In the brain it reaches the hypothalamus to inhibit food intake via the CNS.



Maffei et al (1995) Nat Med 1(11) 1155-1161

Leptin deficiency causing obesity is only relevant in a very small number of patients. What happens is that the increased circulating leptin either desensitises, saturates or destroys the signal transduction pathways of leptin.

Non-Pharmacological Interventions

Lifestyle changes including reducing calorie intake and increasing physical activity. However, this doesn't work chronically (long-term). Note that other drugs can also stimulate increased appetite and contribute to weight gain.

Pharmacological Interventions

Needs to be combined with very low calorie diets and increased exercise. Sibutramine and rimonabant were withdrawn as they had serious side effects including causing cardiovascular disease and suicide, respectively. They all have similar efficacy, which is that they help people reduce 5-10% of their body weight. An ideal drug for obesity should;

- Have a known mechanism of action which reduces body weight
- Benefits should outweigh side-effects
- No addictive properties
- Should be safe to use long-term

Name	Location	Mechanism of Action	Side Effects
Phentermine (Duromine)	Brain	Derivative of amphetamine; displaces NA from storage vesicles which increases [NA] available to bind to the receptors. This suppresses appetite. Can only be used for a max. 12 weeks with dose increases otherwise tolerance is observed. BMI>30.	Increased NA so increased BP, HR, insomnia, nervousness, headache and dry mouth. Cannot be combined with antidepressants and not safe in pregnancy
Orlistat (Xenical)	Stomach, pancreas	Inhibits gastric and pancreatic lipases so decrease dietary fat absorption. It is taken with your meal (3 times a day) to reduce triglycerides. BMI>30. **Note, lipases are released in response to a meal, hydrolyse dietary triglycerides which give smaller components (monoglycerides and fatty acids) which *can* diffuse across mucosal cells.	Explosive diarrhoea and faecal fat leakage. *Must* be combined with a low-fat diet and vitamin supplementation (D&E). Note that the side effects are mostly gastro-intestinal, but a low-fat diet will help side effects significantly.
Glucagon-like peptide-1 agonist (Liraglutide)	Hypothalamus, intestines, liver, stomach fat and muscle	Previously for diabetes patients who experienced weight loss on the drug. Maintenance dose is injected subcutaneously at 3mg (a peptide so this prevents it being destroyed). GLP-1 agonist increases insulin secretion, suppresses glucagon secretion, increases glucose uptake in muscle, slows gastric emptying and reduces appetite.	Nausea, vomiting, diarrhoea, injection site reactions, small increase in HR. Side effects are reduced by slowly increasing the dose from 0.6mg → 3mg. Severe case is pancreatitis. Cannot be taken together with injected insulin otherwise might cause hypoglycaemia → coma

Lecture 23 – Drugs for Dependence

Definitions

Note, not everyone who uses these drugs will become dependent. Dependence is related to the *rewarding* effect of the drug, but also social considerations, administration routes, intention, genetics, etc. An addictive drug will increase dopamine levels in the mesolimbic pathway, which signals a positive reinforcement pathway. This pathway used to be an evolutionary response which helped us survive. **Tolerance** is where you need more drug for the same effects.

- **Drug dependence** – state where drug taking becomes compulsive, taking precedence over other needs
- **Drug abuse** – use of illicit substances (or legal drugs used illicitly) characterised by recurrent and adverse consequences
- **Psychological dependence** – craving, the main reason why people relapse. It is not a physical syndrome
- **Physical dependence** – withdrawal syndrome consisting of physical symptoms when a drug is ceased abruptly
- **Habituation or adaptation** – aversion of negative symptoms or *physical* dependence (called **abstinence syndrome**)

Pharmacology – PHRM20001 – Lecture Notes

Reward Pathways

Are in the **dopaminergic mesolimibic** pathways. The release of dopamine in the **nucleus accumbens** signals to the ventral tegmental area, where excitatory (glutamatergic) signals are sent to the prefrontal cortex, amygdala and hippocampus. Transmitters modulating dopaminergic transmission is not just dopamine! Serotonin, noradrenaline, GABA, opioids and glutamate all have a role to play in these reward pathways.

If you are constantly stimulating these pathways, then you get dependence. E.g. you might have an excess of dopamine being use which results in a decrease if the activity of tyrosine hydroxylase i.e. reduces the synthesis of dopamine. After chronic use, there are other changes such as an increase of dopamine reuptake transporter (to try remove more of the dopamine) and fewer post-synaptic receptors. When you get these structural changes, without the drug you don't have enough dopamine and you get withdrawal.

Routes of Administration

Administration routes of the drug can significantly alter plasma concentration (and therefore, alter the level of intoxication) of the same drug which is taken. E.g. compare IV, smoking, nasal and oral administration. Plasma concentration (and toxicity) is highest with IV. Toxicity is higher when smoked compared with nasal administration which actually has a higher plasma concentration when administered.

CNS Stimulants

There are two overlapping classes, both have specific effects by increasing noradrenaline, dopamine and serotonin. In the past, they were used legitimately to fight fatigue e.g. war airplane fliers were given amphetamines;

1. **Stimulants –** produce excitement, euphoria and reduce fatigue e.g. amphetamine, cocaine AND ecstasy
2. **Psychotomimetics –** affects patterns and perceptions, containing hallucinogens and psychedelics e.g. LSD, ecstasy

Drug Name	Effect	Side effects
COCAINE *Blocks reuptake of NA in the periphery but blocks all three in the CNS	Traditionally chewed plant for fatigue, hunger and altitude sickness. There are reports of psychological, but no physical dependence. In Western Society it is rapidly absorbed at a high concentration resulting in; - Intense euphoria - Increased locomotor activity - Suppressed appetite (increase in DA, NA, 5-HT) - Local anaesthetic properties by blocking Na channels, decrease in AP transmission - Followed by 'crash' irritability, 'cocaine blues'	Craving for more drug. Tolerance and dependence is common, resulting in higher doses being used and an intense abstinence syndrome. Overdose causes hypertension, tachycardia, psychotic symptoms, convulsions, heart arrhythmia.
AMPHETAMINE *Increase exocytosis of NA in the periphery but increases all three in the CNS	Effects vary but includes mood elevation, euphoria, increased locomotor activity and stereotypic behaviour. Also shown to postpone fatigue, cause alertness and confidence. Speedy performance but less accurate - Appetite suppressant - Oral analogues, low doses used for ADHD	Craving, tolerance and dependence is common. Overdose can cause hypertension, tachycardia, psychotic symptoms, convulsions, heart arrhythmia.
ECSTASY (MDMA) Indirectly acting sympathomimetic amine and releases NA through non-voltage dependent Ca^{2+} channel	Taken orally, so you don't get the rush but gives you feelings of love, closeness and empathy. Very similar to amphetamine (just has an extra methyl group from methamphetamine). Also releases dopamine and serotonin from the brain so you get the tolerance, addiction and appetite suppressant. More of a psychological dependence than physical addiction	Increase in heartbeat, tremor, tachycardia, nervousness, psychosis. You can also get disruption in thermoregulation (from chills to sweating) resulting in sweating and over intoxication from drinking water.
LSD A derivative of a fungus. An agonist at 5-HT receptors.	A psychotomimetic causing visual, auditory and tactile hallucinations. Cognition is disturbed but the person remains aware they have taken the drug. Judgement is impaired. Can results in 'bad trip' if they are depressed or anxious at the time etc.	Homicide, suicide attempts. Rapid tolerance (And cross tolerance with other psychotomimetic)

CNS Depressants

Drug Name	Effect	Side effects
CANNABIS Agonist of cannabinoid receptors for inhibition of adenylate cyclase resulting in an increase of dopamine release	Extracts of the hemp plant, active ingredient is THC. Subjective effects but the common effects include; - Relaxation, well-being without aggression - Sharpened sensory awareness - Increased intensity of sounds and sights - Impaired short-term memory and coordination - Increased appetite	Tachycardia, vasodilation, catalepsy, reduced intraocular pressure (bloodshot eyes), bronchodilation. Used in cancer patients to increase appetite and is an antiemetic (anti-vomiting)
ETHANOL Inhibits Ca^{2+} channels, enhances GABA action and inhibits glutamate receptors	Behavioural (limbic, prefrontal cortex system) effects includes increased self-confidence and euphoria. At higher doses causes mood swings and aggression. Motor (cerebellum) effects includes loss of motor coordination and slurred speech. Tissue effects include cardiovascular protection, liver damage, neurodegeneration and foetal impairment	Marked tolerance (cytochrome P450 becomes more efficient at metabolising alcohol) and well-defined abstinence syndrome. *NMDA channels are the glutamate receptors. An increase in glutamate signalling can lead to convulsions, so withdrawal can result in seizures.

Lecture 24 – Drugs for Pain

Pain Basics and definitions

There is acute, inflammatory and chronic pain. Pain is described as the "unpleasant sensory and emotional experience associated with actual or potential tissue damage".

- **Acute pain** - recent onsets with limited duration, either somatic (sharp, localised) or visceral (dull)
- **Chronic pain –** either has a nociceptive basis (e.g. cancer), neuropathological basis (e.g. neuralgia, neuropathy) or idiopathic pain (pathogenesis not well accepted or understood e.g. spinal pain)

Type of chronic pain is summarised in the adjacent table; nociceptive superficial and somatic, nociceptive deep and somatic, nociceptive visceral and neuropathic. Neuropathic refers to damage to nociceptive pathways where something which shouldn't be causing pain does e.g. burning, shooting pain.

	Nociceptive - superficial somatic	Nociceptive - deep somatic	Nociceptive - visceral	Neuropathic
Stimulus origin	skin, subcutaneous tissue; mucosa of mouth, etc.	bones, muscles, joints; organ capsules, pleura	solid or hollow organs; deep tumour masses	damage to nociceptive pathways
Examples	malignant ulcers	bone metastases; liver capsule distension or inflammation	deep abdominal or chest masses; intestinal, biliary colic	tumour-related: spinal cord compression, brachial plexus non-tumour-related: post-herpes neuralgia, phantom pain
Description	hot burning stinging	dull aching	dull deep	"pins & needles", tingling, burning, shooting; allodynia; phantom pain

Overview of the nociceptive circuit

(1) Activates the peripheral terminal by noxious stimulus
(2) Action potentials conducted to dorsal horn (gateway of pain where signals of pain can be dampened or amplified)
(3) Dorsal horn relays signal to CNS neurons
(4) Signals pass through brainstem, thalamus and cortex
(5) Descending modulatory control pathway initiated

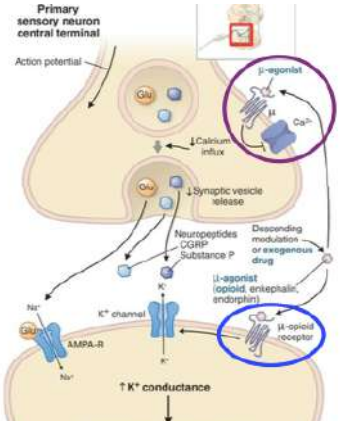
Pharmacological treatment

For *acute* pain we use pains scores. Mild pain (paracetamol), moderate pain (paracetamol, NSAID, or oral opioid) and severe pain (oral opioid or opioid or fentanyl patch).

Opioids

Obtained from unripe poppy seed capsules which acts on the miu-opioid receptor to cause analgesia, euphoria, dependence and constipation. Morphine, codeine and heroin are all opioid derivatives (methadone and fentanyl are synthetic opioid compounds). Note, the single antagonist to remember is **naloxone** which is an antagonist for the miu-opioid receptor

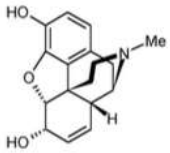
So ordinarily in your body, you have endorphins (e.g. beta-endorphin, encephalin, dynorphin) which is synthesised and released from nerves through the brain, spinal cord and GIT. They will help with analgesia and intestinal motility by acting on the opioid receptors when your body deems necessary. These aren't useful as therapeutic agents as they aren't absorbed, are quickly metabolised and don't pass through the blood brain barrier.



Miu Opioid Gi-GPCRs

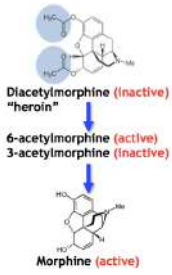
If you want to cause analgesia, then you want to target the miu-opioid receptor as it has a dense population in the brain, spinal cord and peripheral tissues. They are at interneurons and descending inhibitory fibres to inhibit **central relaying of nociceptive** stimuli. Therefore, if you want to inhibit peripheral nerve transmission or inhibit at the dorsal horn then you want a **miu-opioid agonist.** There are three acting types;

1. **Presynaptic –** inhibition of Ca+ influx of the action potential to decrease the neurotransmitter release at the nociceptive nerve terminals
2. **Postsynaptic –** miu-opioid receptor activation which increases K+ conductance which hyperpolarises i.e. less likely to respond to any excitatory neurotransmission.
   ***Enhancing descending modulatory pathways –** miu-opioid agonists also enhance activity of the inhibitory control pathways



Example #1 Morphine

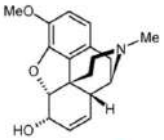
A miu-opioid agonist which causes analgesia, euphoria, respiratory depression, nausea, vomiting, miosis and antitussive actions. *__Antitussive__ means cough suppression and __miosis__ means pupillary constriction. At the periphery it causes constipation as activity at __myenteric neurons__ decreases, less ACh released so there is less motility. There is also often orthostatic hypotension and histamine release from mast cells triggering asthma / vasodilatation.



Usually given intravenously or intramuscular because otherwise it is metabolised and has poor CNS entry. It has a plasma half-life of 3-6 hours unless it is given in slow-release oral tablets. Can cause tolerance (ironically doesn't affect constipation or miosis) and dependence on the drug, with a distinguishable abstinence syndrome. Craving from psychological dependence can last for months or years.

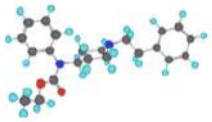
Example #2 Heroin

Highly lipid-soluble pro-drug which has a more rapid entry into the CNS than morphine which makes it more addictive. Results in fast, strong activation of pleasure centre and euphoria.



Example #3 Codeine

Methylmorphine which makes it less potent than morphine. Orally active, causes constipation but not euphoria or respiratory depression. Even acts as an antitussive at sub-analgesic Doses



Example #4 Fentanyl

Short-acting but extremely potent and highly lipid-soluble. Used for incident or procedure-related pain e.g. burns. Needs to be administered intramuscularly, often through a patch if it needs to be longer-acting. It is the least constipating opioid. Long half=life despite short-acting from redistribution out of inactive stores.

Opiate addicts

#1 **Diamorphine –** heroine in an injectable form, also prescribed for general medical conditions in the UK
#2 **Methadone –** orally active, slow onset, long half-life with a less intense (but more prolonged) withdrawal reaction
#3 **Naxolone –** used to treat opioid overdose as it is an opioid receptor antagonist. It needs to be given intravenously as it does experience rapid hepatic metabolism. It has a half-life of only an hour

Opioid Point Summary

- Used for moderate to severe pain, for surgery and trauma
- Does have medical uses such as in myocardial infarctions where a circulatory depression is needed
- Works in 1/3 patients and may only decrease the pain by 30-50% at best
- 80% of patients takings opioids will experience at least one adverse effect

Lecture 25 – Drugs for Depression

Mood Disorders

Two broad classifications of official mood disorders; *Therapy is best when pharmacological treatment is paired with cognitive and behavioural therapy. Drugs will be mixed up (though interactions need to be known) to treat correct cause.

- Classed as a major **depressive** disorder includes sustained (at least 2 weeks) of symptoms excluding manic episodes. People with depressive disorders can be paired with anxiety, including generalised anxiety disorder for panic attacks. 40-50% of patients don't respond to anti-depressive drugs.
- **Bipolar** disorder includes sustained at least 1 week) extreme melancholia, extremely elation and hyper excitability. Depressive periods are more frequent than the periods of elevated mood. Includes symptoms of mania (or hypomania) e.g. spending lots of money without recognising the consequences of their actions until after episode

Categories of Major Depressive Disorder pharmacological treatment

The beneficial effects may not become apparent until 1-3 weeks of treatment with optimal effects around 6-8 weeks. Patients will experience side effects in the 'waiting' weeks. Serendipity has played a major role in the discovery of most of these drugs e.g. tricyclic antidepressants.

Category of Drug	Example	Effect	Side Effects
Tricyclic Antidepressant	Amitriptyline	Used for neuralgia, post-herpetic pains and depression. Inhibitors of neuronal uptake of NA (and 5-HT in higher concentrations). Also an antagonist at alpha-1 adrenoceptors, muscarinic, histamine and 5-HT receptors when in high concentrations (tranquiliser)	Anti-cholinergic (anti-SLUD effects including dry mouth, blurred vision, urinary retention, constipation), cardiovascular blockages, postural hypotension, CNS effects, weight gain
"Second Generation" Antidepressants – SSRIs	Fluoxetine, sertraline, escitalopram	Selective inhibitor of serotonin uptake	Insomnia, GIT disturbances, sexual dysfunction, restlessness.
"Second Generation" Antidepressants	Venlafaxine	Not discussed	Fewer side effects than TCA which is why they became more popular.
Monoamine Oxidase Inhibitors (MAOI)	Moclobemide	Increase levels of NA, 5-HT and DA. **If you block MAO then you get tyramine build-up which is an indirectly acting sympathomimetic effects causing hypertension. Moclobemide is the only reversible, therefore less effects.	Dizziness, nausea, insomnia. Not advised to be used long-term as they can kill people when combined with cheese, red wine, chocolate, bananas, (anything containing tyramine)

Studies have shown that the drugs work because they cause adaptive changes in receptors rather than changing neurotransmitter levels specifically.

Pharmacological Treatment of Bipolar Affective Disorder

**Phenothiazine have similar structure to the TCAs but they act as tranquilisers and anti-psychotics, used for major psychotic illnesses such as schizophrenia. In the case of lithium, the mechanism of action is unknown.

Category of Drug	Example	Effect	Side Effects
Bipolar disorder drugs	Lithium (carbonate)	Mood-stabilisers. Low therapeutic index (2-3).	Plasma levels must be monitored regularly to avoid serious toxicity. Side effects are renal, thyroid and neurological.
Antiepileptic drugs	N/A	Mood-stabilisers - can also be effective in bipolar disorder so they function as an alternative treatment	Not discussed
Antipsychotic drugs	N/A	Calms people down during manic phases and maintains a base level of sedation. Often combined with a depressive disorder drug.	Not discussed