2.5 Pharmaceutical Chemistry

Drugs are substances which alter the biochemical processes of the body from their *normal* state.

- Drugs with a beneficial effect are called medicines.
    - Painkiller medicines e.g. aspirin
    - Antibiotic medicines to kill bacterial infection e.g. penicillin
    - Anti-asthma medicines to open airways e.g. salbutamol
- Drugs are described as pharmacologically active
    - Pharmacology is the study of how drugs effect living organisms and the development of new and better medicines.
- The pharmaceutical industry is big business in the UK
    - Companies invest huge sums in drug development
    - A 25 year exclusive patent of a drug will give around 15 years of exclusive profits once clinical trials declare the drug to be safe to humans (proving a drug is safe to humans usually takes around 10 years of the 25 year exclusive patent period)
- Humans have always tried to find cures for illnesses and ailments
    - South American tribes discovered chewing bark from the Cinchona tree, found in Peru, lowered temperature
        - Fever symptoms of malaria relieved due to presence of quinine, from the tree bark
        - Quinine is now a standard precaution for people at risk of exposure to malaria
    - Ancient Egyptians would take opium for treatment of pain
    - Castor oil was taken for the treatment of parasitic worms

Until the late 19th Century, medicines were almost always plant extracts

- Plants would be soaked in water or boiled
- Many herbal remedies offer an alternate to conventional medicines

Modern chemistry allows pharmacologically active ingredients to be isolated and identified

- The active ingredient can then be synthesised, often cheaply
- The active ingredient can indeed be improved by altering the structure to
    - To make the active ingredient more potent
    - To reduce any side-effects the drug may have

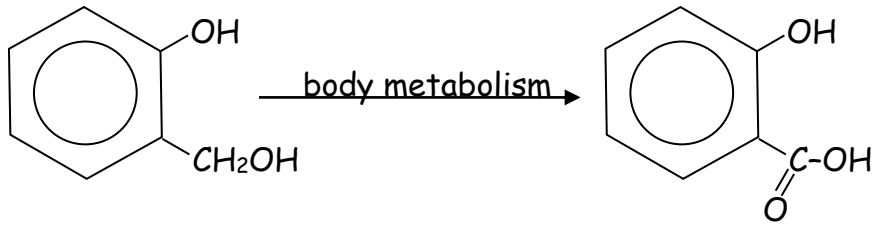
Development of Aspirin

In ancient Greece, extract of Willow bark was used to relieve the pain of child birth

- The Romans would boil Willow with vinegar for use as a pain remedy

The active ingredient in Willow bark was isolated by Leroux in 1829.

- Active ingredient was called salicin.
- Hydrolysis of salicin gives glucose and salicylic alcohol
- Salicylic alcohol is metabolised by the body to form salicylic acid (2-hydroxybenzoic acid)

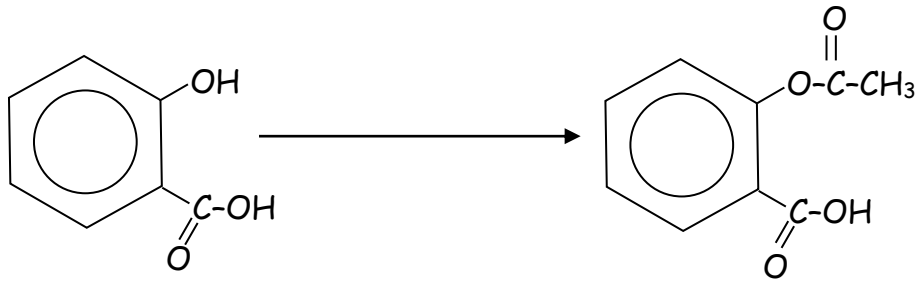


salicylic alcohol

salicylic acid
(2-hydroxybenzoic acid)

- Salicylic acid was used as a pain-relieving drug (an analgesic)
  - Also as an fever-reducing drug (an antipyretic)

- Salicylic acid also causes serious irritation of the stomach lining
  - Leads to stomach, intestine and mouth ulcers
  - Derivative of salicyclic acid developed to reduce stomach lining irritation



salicylic acid
(2-hydroxybenzoic acid)

acetylsalicylic acid (aspirin)
(2-ethanoylhydroxybenzoic acid)

Salicylic acid was synthetically produced by reacting benzene with carbon dioxide

- this was first achieved by Felix Hoffman, an employee of the Bayer Chemical Company
- aspirin was released onto the market in 1899.

Aspirin is an extremely well known drug with the following properties:

- analgesic effect (painkiller)
- antipyretic effect (fever/temperature-reducing)
- anti-inflammatory effect (used to help treat arthritis)
- aspirin also reduced the tendency of the blood to clot by preventing platelets from aggregating. Used in small quanitities by survivors of heart-attacks.

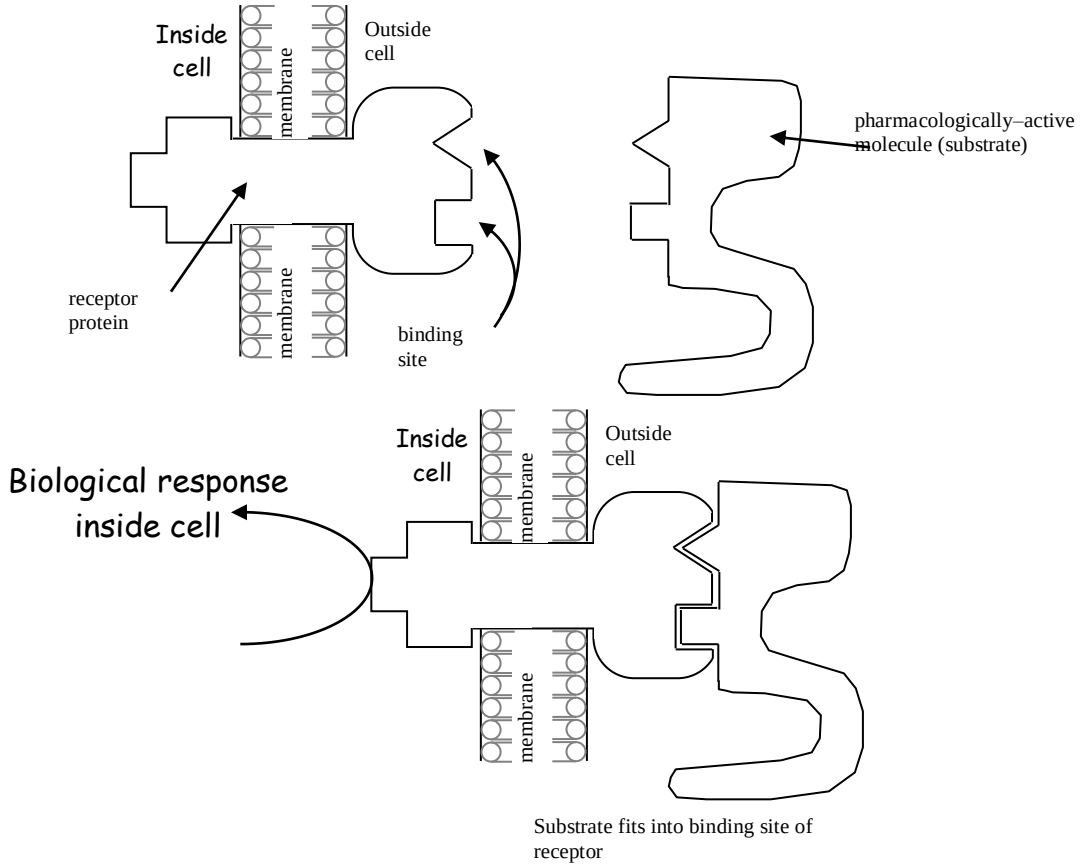
Aspirin works by blocking an exzyme called cyclooxygenase

- the production of chemicals called prostaglandins is prevented
- prostaglandins are chemicals involved in fever, pain and inflammation in the body
- Aspirin is classed as a Non-Steriodal Anti-Infammatory Drug (NSAID)
    - Other NSAID medicines include Ketoprofen, Ibuprofen.

How Medicines Work

Medicines work by binding to a receptor in the membrane of a cell

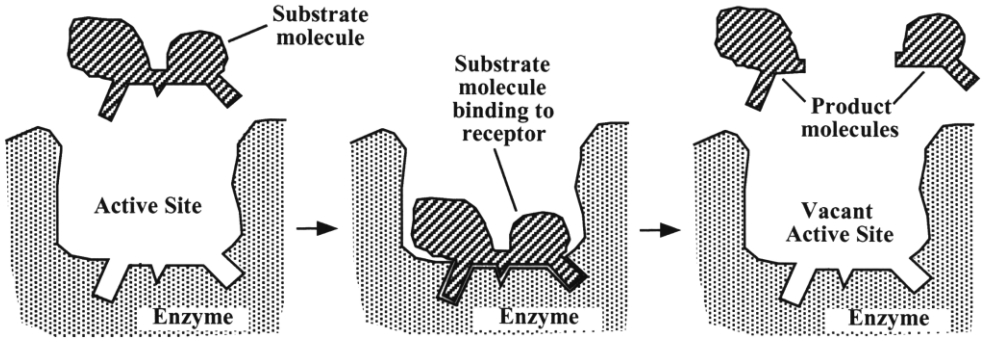
- Receptors are proteins which straddle the membrane in cells
- Receptors can also be enzymes, which catalyse reactions found inside cells. These receptors are known as catalytic receptors. The medicine would need to be able to cross the cell membrane into the cell.



- Weak forces of attraction such as hydrogen bonding and polar attractions lead to pharmacologically-active molecule entering binding site and reversibly binding to receptor protein molecule
- This interaction stimulates a biological response inside the cell
- The active molecule (substrate) then unbinds from the receptor protein and leaves the site chemically unchanged
    - The body's metabolism will remove the molecule from the system.

The active site of enzymes is very similar to the binding site of a receptor molecule

- If the substrate does not exactly fit the active site, then there will be no response.



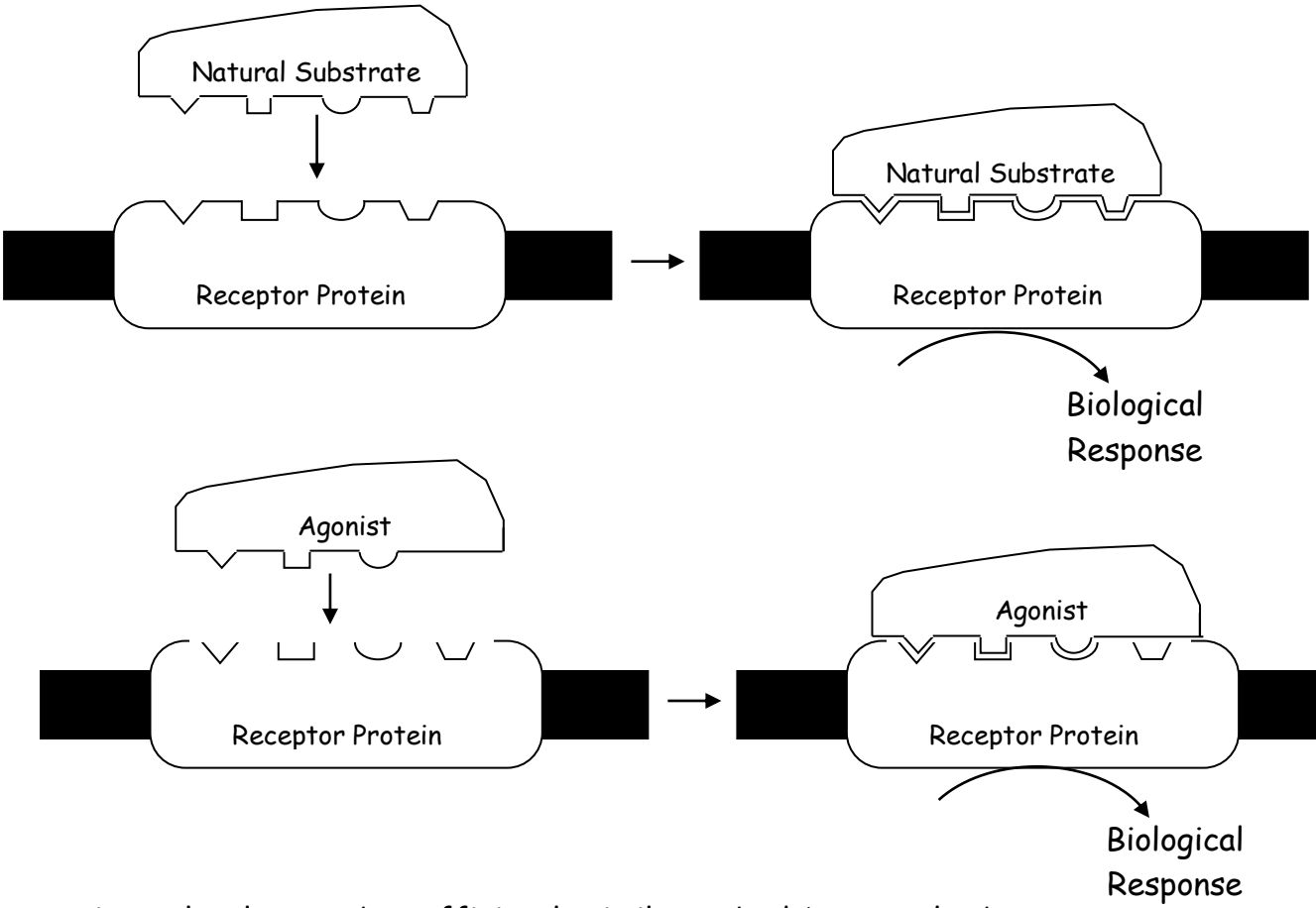
Agonists and Antagonists

Medicines work by acting on the binding/active sites of receptors/enzymes. There are 2 main ways medicines interacts with receptors and enzymes

- Medicines mimic the substrate molecule and trigger the biological response inside the cell
- Medicines bind the receptor/enzyme and block any other molecules from binding with the receptor/enzyme.

a) Agonists

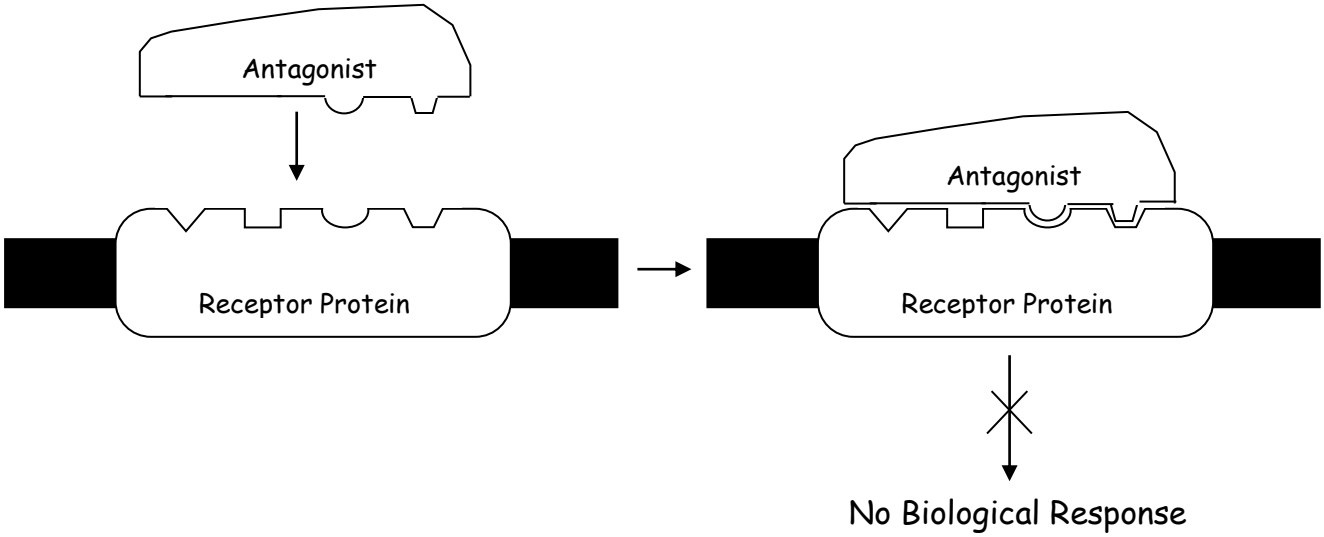
- agonists interact with a receptor proteins binding site
- agonists produce same response as the body's natural substrate



- agonist molecule must be sufficiently similar to body's natural substrate
    - agonist must fit into binding site of receptor
    - must trigger the biological response inside the cell
- an agonist medicine can enhance the body's biological response by
    - the agonist medicine can be in a higher concentration than he body's natural substrate
    - the agonist medicine can have a greater effect than the natural substrate if the agonist medicine lasts longer in the body before metabolism

b) Antagonists

- Antagonists interact with binding site of the receptor protein
- Antagonists do not trigger produce the biological response inside the cell



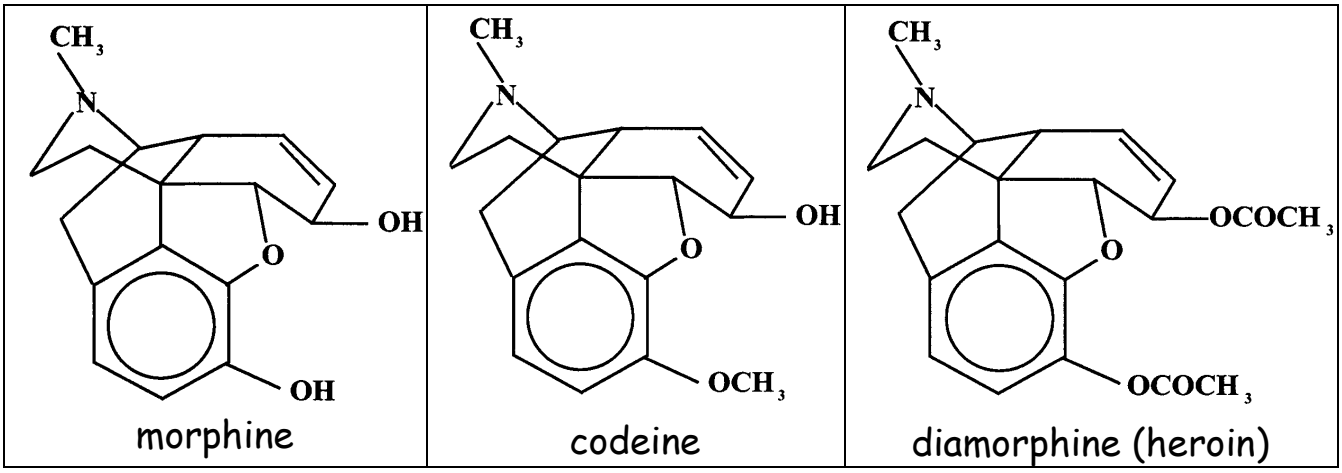
- Antagonists fit the binding site of the receptor protein
    - Antagonists lack the appropriate shape to fully activate the receptor protein
    - No biological response inside the cell
- Antagonists are like a key that fits into the lock but will not turn the lock open
    - Antagonist molecules bound to the receptor protein is similar to the key being in the lock
    - No other molecules can fit into the receptor binding site when the antagonist is bound just like no other key will fit into the lock when there is already a key in the lock
- The body natural substrate is unable to access the binding site while the antagonist is bound to the receptor
    - This reduces the normal level of biological response in the cells
- Antagonists which bind to active site of enzymes are called inhibitors
- Antagonist molecules may have a stronger binding attraction for the binding site than the natural substrate
    - Antagonists may block the natural substrate for quite some time

Pharmacophores

The shape of a medicine molecule is critical in the activity of agonists and antagonists

- The chemical structure of the pharmacologically-active molecule must have a similar 3-d shape as the natural substrate
- The structural fragment that all molecules which fit into the binding site of the receptor protein is called the pharmacophore
    - Natural substrate, agonists and antagonists all contain the pharmacophore's shape within their molecule
- It is the pharmacophore part of the molecules which fits into the binding site of receptors (and active sites of enzymes)

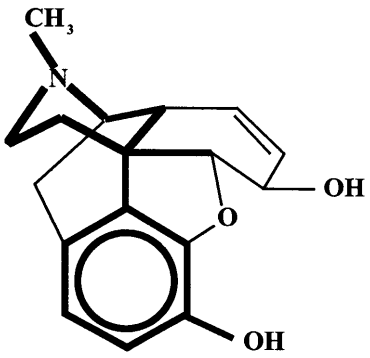
e.g. opiates



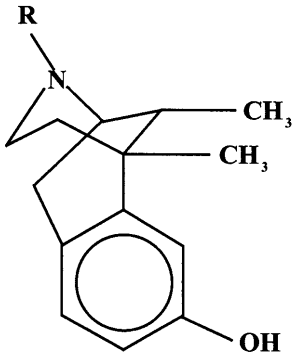
Morphine is a powerful analgesic (painkiller) which is very addictive

- Heroin is a more powerful opiate than morphine
    - Heroin has the same pharmacophore as morphine
    - Heroin is less polar than morphine as the 2 polar –OH groups are esterified
    - Heroin has a more powerful effect morphine as less polar molecules can cross the blood-brain barrier more easily
- Codeine is used in prescription analgesic painkillers
    - Codeine is less potent than morphine and is safer than morphine as there is less risk of addiction
    - Codeine has the same pharmacophore as morphine and heroine and interacts with the same receptor binding site

Scientists make new medicines by keeping the same pharmacophore, but change other chemical groups on the edges of the pharmacophore



Pharmacophore shape



Molecule under investigation

This kind of research can result in:

- The new molecule having a greater attraction for the binding site of the receptor than the natural substrate/other medicines
- The new molecule having a lesser attraction for the binding site than the natural substrate
- The new medicine may be cheaper/easier to syntheses
- The new medicine may have less side-effects elsewhere in the body than previous versions of the medicine
- The new medicine may have a greater specificity for certain areas of the body
    - Receptors for the same natural substrate can have slightly different shapes in various parts of the body.
    - Research can show these receptors are slightly different and are then sub-classified e.g. adrenaline receptors α_1, α_2, β_1, β_2 all bind with adrenaline but will selectively bind with certain compounds and not others
    - New medicine produced may have particular reactivity for one part of the body over another

Pharmacology in Action

1. Asthma and Salbutamol

Adrenaline, called epinephrine is the US, is produced by the adrenal glands in the body, found just above the kidney

Adrenaline has a wide range of pharmacological effects

- Increases heart rate (tachycardia)
- Increases blood pressure (blood vessel constriction)
- Widens the airways (dilates the bronchioles)

During an asthma attack, adrenaline used to be used to open the airways but

- adrenaline increases heart rate (requiring more oxygen)
- adrenaline increases blood pressure

The 2 other effects of adrenaline away from the airways makes adrenaline a risky treatment for asthma during an attack.

With pharmacological research, it was found that the receptors for adrenaline are not identical in the different parts of the body where they are found. The receptors for adrenaline were sub-classified as follows:

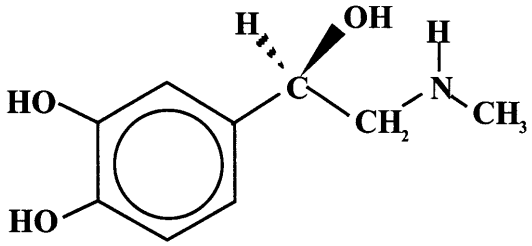
Adrenaline Receptor	Action
α_1	Increased blood pressure by constricting blood vessels
α_2	[don't worry about this one for AH Chemistry]
β_1	Increases the heart rate
β_2	Opens airways by dilating bronchioles

It was obvious that an agonist for β_2 adrenaline receptors could be a viable, specific treatment for asthma attacks

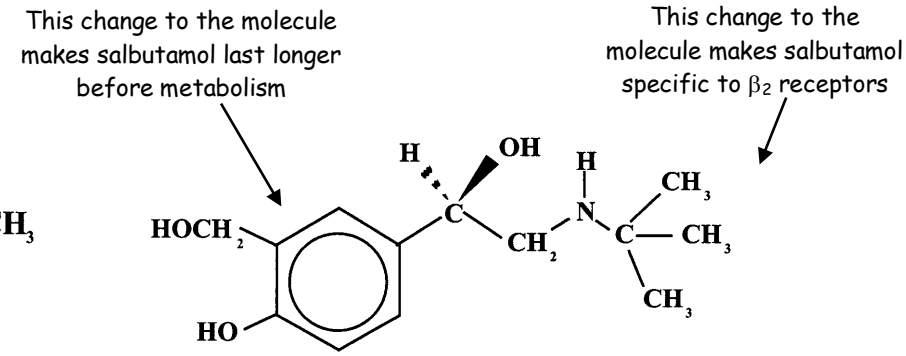
- if α_1 and β_1 adrenaline receptors are not stimulated at same time then blood pressure and heart rate are unaffected.
- Adrenaline triggers all three responses at same time

Salbutamol (called Ventolin commercially) has a similar shape in one part of the molecule to adrenaline

- Adrenaline and salbutamol have the same pharmacophore for β_2 adrenaline receptors



Adrenaline



Salbutamol

Salbutamol has the same pharmacophore as adrenaline for β_2 adrenaline receptors

- salbutamol can be used as an aerosol in an inhaler for quick application
- salbutamol is described as a bronchiodilator

Other Applications of Adrenaline Receptors

a) Beta Blockers

- β_1 agonists would increase heart rate and β_1 antagonists should slow heart rate
- β_1 antagonists like propranolol and atenalol slow the heart rate
- β_1 antagonists work by binding to β_1 adrenaline receptors but do not trigger the biological response, increasing the heart rate.
- Adrenaline cannot bind with β_1 receptors if antagonist is already in binding site

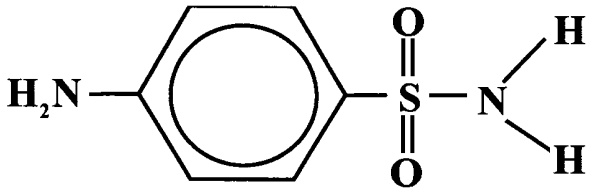
b) Blood Pressure

- If α_1 agonists increase blood pressure by narrowing the diameter of blood vessels, then α_1 antagonists will dilate blood vessels and reduce blood pressure

2. Antibiotics – Sulphonamides

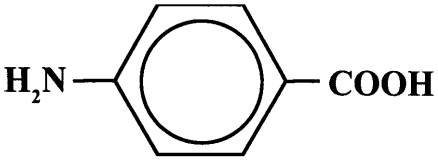
The first antibiotic medicines were derived from dyes

- Paul Ehrlich was first to use sulphonamides as an antibiotic in 1933
- The body's metabolism breaks down the down the dye to produce the active ingredient sulphanilamide



sulphanilamide

- Sulphanilamide blocks the synthesis of the essential vitamin – Folic Acid in bacteria
  - Bacteria are able to synthesize the essential vitamin folic acid from and enzyme in the bacteria
  - Sulphanilamide blocks the enzyme required stopping the bacteria from making folic acid
  - The natural substrate for this enzyme is 4-aminobenzoic acid
    - Sulphanilamide has a similar shape to 4-amino benzoic acid



4-aminobenzoic acid

  - bacteria are unable to multiply without enough folic acid and bacterial reproductions stops

- humans lack the enzyme to make folic acid and absorb folic acid through their diet.
  - Humans are unaffected by sulphonamide medicines like sulphanilamide

- Sulphonamides are bacteriostatic agents
  - Sulphonamides do not reduce the number of bacteria
  - Sulphonamides stop the further growth of bacteria

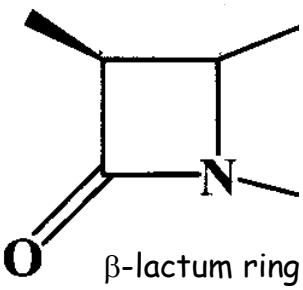
3. Antibiotics – Penicillins

Penicillin was discovered by Alexander Fleming in 1928

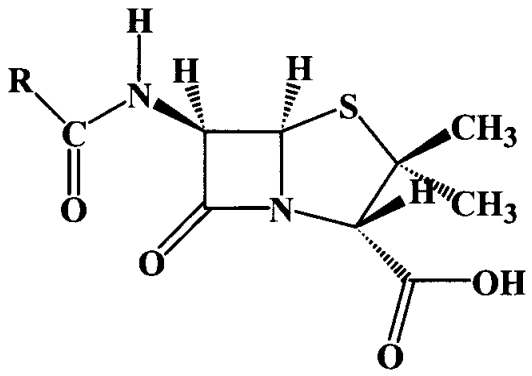
- It was ~1940 before Penicillin G was isolated by Florey & Chain

All penicillins contain the β-lactum ring structure (the pharmacophore)

- Penicillins have a very similar structure
- Main differences are to the R group on diagram below



β-lactum ring



basic penicillin structure

Penicillins are bactericidal agents

- penicillins kill bacteria
- penicillins inhibit the synthesis of cross-links between polymer chains sticking out of bacterial cell walls
- bacterial cell walls lack the necessary strength and the bacteria bursts and dies
- penicillins block the enzyme which crosslinks the cell wall polymers in bacteria
    - penicillins act as antagonists
- animal cells do not have cell walls so are unaffected by penicillin

However,

- Bacteria continue to evolve and mutate. Bacteria are becoming more and more resistant to the commonly used antibiotics like penicillins and sulphonamides e.g. MSRA bacteria (aka superbugs)
    - After a period of time where antibiotic research stood still as there were enough antibiotics to treat bacterial infections, much research has begun to develop new antibiotics to treat the resistant bacteria
    - It is important that antibiotics are used sparingly and not over used
        - Overuse allow bacteria to develop resistance
    - Antibiotics are useless at treating viruses
    - When prescribed antibiotics, the full course of the medicine must be consumed, regardless of the stage of recovery (i.e. I feel better so I'll stop taking it)
        - Bacteria infection must be wiped out so no bacteria survive.
        - Bacteria which survive *may* go on to development antibiotic resistance

Drug Quantities

Pharmaceutical preparations are often composed of many and varying ingredients. These ingredients can take various solid or liquid forms and different methods of describing concentrations need to be taken into consideration.
A medicinal product needs to be defined by its concentration as it is this concentration that lets someone know how much of the drug is present.

- ***Solid ingredients in solid tablets can often be described as a weight / weight percentage where***
  1% w/w is equivalent to 1g of ingredient for every 100g of tablet

  Example 1: *5g of a cream contains 250 mg of sulphur in yellow soft paraffin.*

  It would be considered as a solid within a solid ∴ w/w.
  Before comparing, they must be in the same unit, 250 mg = 0.25g.

$$\frac{250mg}{5g} \times 100 = \frac{0.25g}{5g} \times 100 \quad = 5\% \text{ w/w}$$

- ***Solid ingredients suspended in a liquid (suspension) can often be described as a weight / volume percentage where***
  1% w/v is equivalent to 1g of ingredient for every 100 ml of suspension

  Example 2: *An eye wash contains 1.2 g of sodium chloride dissolved in water to produce 120 ml of solution. Express the concentration of the solution as amount strength.*

  It would be considered as a solid within a solution, so w/v.
  - *Before comparing, they should strictly be expressed in the 'same unit'. For simplicity, it is assumed that 120 ml of solution (water) would be equivalent to 120 g.)*

$$\frac{1.2g}{120ml} \times 100 = \frac{1.2g}{120g} \times 100 \quad = 1\% \text{ w/v}$$

- ***Liquid ingredients in solutions can often be described as a volume / volume percentage where***
  1% v/v is equivalent to 1ml of ingredient for every 100 ml of solution

  Example 3: *2 litres of a cough mixture solution contains 50 ml of ethanol.*

It would be considered as a liquid within a liquid, so v/v.

- *Before comparing, they must be in the same unit, 2l = 2000 ml*

$$\frac{50ml}{2\ litres} \times 100 = \frac{50ml}{2000ml} \times 100 = 2.5\%\ v/v$$

Example 4: *A patient is injected with 1% w/v morphine sulphate. The required dose of morphine sulphate is 20 mg. What volume should be injected into the patient?*

1 % w/v morphine sulphate = 1 g per 100 ml

1g	⟷	100ml morphine sulphate
1000mg	⟷	100ml
20mg	⟷	100ml x $^{20}/_{1000}$
		=2ml morphine sulphate

Example 5: *How many milligrams of aluminium acetate are required to prepare 500ml of a 0.03% w/v solution?*

0.03 % w/v aluminium acetate = 0.03 g per 100 ml

0.03g	⟷	100ml aluminium acetate
30mg	⟷	100ml
30mg x $^{500}/_{100}$	⟷	500ml
= 150mg		

Example 6: *During a synthesis a student pipetted 10 cm^3 of a 5% solution of ethanol into the reaction vessel. The % solution by mass refers to grams of solute in 100 cm^3 of solution.*
Calculate the number of moles of ethanol added to the synthesis.

5% ethanol solution = 5g ethanol in 100ml solution

5g ethanol	⟷	100ml solution
0.5g ethanol	⟷	10 ml solution

1mol C_2H_5OH = (2x12)+(6x1)+(1x16) = 24+6+16 = 46g

$$\text{no of mol} = \frac{\textbf{mass}}{\textbf{gfm}} = \frac{0.5}{46} = 0.011mol$$

Notice that these methods of dealing with concentrations do not require knowledge of the formulae of substances, the gram formula mass or any knowledge of the mole concept.

As part of clinical studies, chemists may need to measure the amount of a drug present in a patient over many days. *These quantities will be very small (compared to the quantity of sample taken) and will often be measured in a unit called* ***parts per million*** *(ppm).*

Parts per million means there is a 10^6 difference between the unit used to describe the quantity of chemical being analysed and the unit used to describe the quantity of sample.

For example: ***mg ($m=10^{-3}$)*** ***per kg (10^3)*** (*used commonly*)
mg ($m=10^{-3}$) ***per litre (10^3)*** (*used commonly*)
ng ($n=10^{-9}$) ***per mg ($m=10^{-3}$)***
g (10^0) ***per tonne (10^6)***

One way of calculating a concentration in parts per million is to put both quantities into the same unit and multiple by 1,000,000:

$$\text{parts per million} = \frac{\text{quantity of chemical}}{\text{quantity of sample}} \times 1000000$$

Example 7: *A 1.5 g tablet contains 7.2 mg of active ingredient. Express this in parts per million.*

$$\text{parts per million} = \frac{7.2\text{mg}}{1.5\text{g}} \times 1{,}000{,}000 = \frac{7.2\text{mg}}{1500\text{mg}} \times 1{,}000{,}000 = 4800\text{ppm}$$