GENERAL PHARMACOLOGY

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CONTENTS

This chapter includes a review of:

- Pharmacokinetic factors
- Drug movement across membrane barriers
- Pharmacokinetics
- Pharmacodynamics

INTRODUCTION

Pharmacokinetics can be described as the study of the time course of the absorption, distribution, metabolism and elimination.

- In effect what the drug does to the body
    - Absorption, modification, detoxification, excretion

The interactions between a drug and the biological system are described as:

a. Pharmacodynamic – the effects of the drug on the body at receptor level
b. Pharmacokinetic – the way in which the body handles the drug

PHARMACOKINETIC FACTORS

Absorption depends on molecular properties of drug (how easily it is absorbed by each tissue), viscosity of its vehicle (considering eye medication – ocular surface contact time), functional status of the tissue forming the barrier to penetration. Drug distribution over time can usually be predicted by interrelationships and compartments of barriers (blood aqueous barrier). Metabolism (how drug is used by body) plays an important role in eliminating drugs and their sometimes toxic by-products from the body.

a. Absorption (how the drug enters the body)
b. Distribution (how the drug is disseminated throughout the bodily tissues and fluids)
c. Metabolism (how the drug is broken down and used by the body)
d. Excretion (elimination of the drug)

DRUG MOVEMENT ACROSS MEMBRANE BARRIERS

Most drugs must pass across a lipid soluble membrane at some point therefore dual solubility is required.

Dual solubility requirement for most drugs i.e. water soluble to dissolve in body fluids like blood plasma or aqueous humour and lipid soluble to pass across lipid membranes (e.g. tears). Most drugs move by passive diffusion.

Absorption of drugs can be passive or active. Passive transport is enhanced by a greater area for absorption, high concentration gradient and increased contact time.

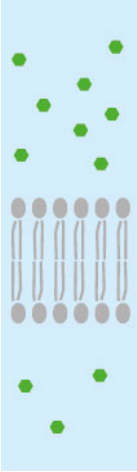
- Passive diffusion
- Facilitated passive diffusion
- Active transport
- Pinocytosis (polypeptide drugs)

PASSIVE DIFFUSION

Solute dissolves in solution to form solvent. Simple diffusion occurs from an area of high concentration to one of low concentration, e.g. GI tract to blood. Most drugs are weak organic acids or bases. They can occur in ionized or unionized forms in aqueous solution. Unionized forms are lipid soluble. Ionized forms are usually lipid water soluble and have a high electrical resistance – charge on cell surface.

When given through most routes (except intra-venously), a drug must traverse several semi-permeable membranes before reaching systemic circulation. Biological barriers selectively inhibit passage of the drug molecule – mainly cholesterol and phospholipids. The essential fact to know is that highly ionized drugs cannnot cross lipid membranes (basically they can't go anywhere) and unionised drugs can cross freely. Morphine is highly ionised, while fentanyl is the opposite. Consequently the latter has a faster onset of action.

- Depends on concentration of solute
- Rate depends on concentration gradient, lipid solubility, ionisation, size and area of absorption
- If cell membrane is lipid – diffusion more readily occurs if lipid soluble drug



***F*igure 2.1 (a) Diagram showing a double phospholipid membrane and some molecules in solution**

The driving force is the drug concentration gradient described by Fick's law:

Flux = (C1 – C2) – (Area x Permeability Coefficient) / Membrane Thickness

- Flux describes the number of molecules moved across the biological barrier per unit time
- C1 is the higher drug concentration and C2 the lower drug concentration
- Area quantifies the surface area across which diffusion occurs
- Permeability coefficient — a numerical value describing mobility of a particular drug across that diffusion barrier
- Membrane thickness — a measure of the thickness of the particular membrane barrier which the molecules are transported across

Drug concentration gradient is manipulated in:

- the treatment of infectious keratitis through the use of high concentration highly fortified antibiotic solutions

High concentration highly fortified antibiotic solutions:

  - drive the movement of the antibiotic drug molecules into the infected cornea along the concentration gradient`, and
  - ensure rapid drug delivery of high concentrations of the pharmaceutical

FACILITATED PASSIVE DIFFUSION

With certain molecules (e.g. glucose), the rate of membrane penetration is greater than expected from their low lipid solubility. May be due to a carrier component, carrier-mediated diffusion is characterized by selectivity and saturability. The carrier transports only substrates with a relatively specific molecular configuration, and the process is limited by the availability of carriers. The process does not require energy expenditure, and transport against a concentration gradient does not occur.

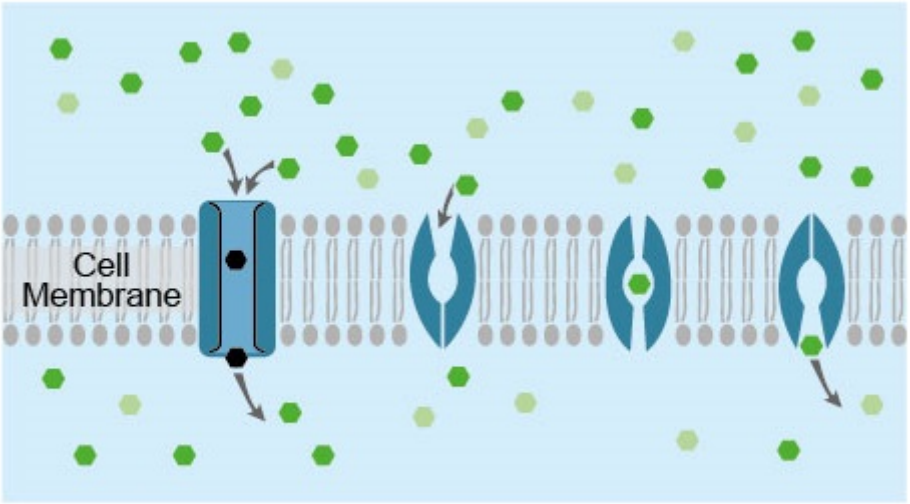


***Figure 2.2 Selectivity** in facilitated passive diffusion – specific molecules are **available** for binding to the drug/molecule carrier*

ACTIVE TRANSPORT

This process is characterized by selectivity and saturability and requires energy expenditure by the cell (fig. 2.3). Substrates may accumulate intra-cellularly against a concentration gradient. Active transport appears to be limited to drugs structurally similar to endogenous substances. These drugs are usually absorbed from sites in the small intestine. Active transport processes have been identified for various vitamins, sugars, and amino acids.

Only specific and a limited amount of some specific these drugs/molecules at once can be transported this way. Drugs may move into a cell against a concentration gradient, i.e. there may be more drug inside the cell that outside.

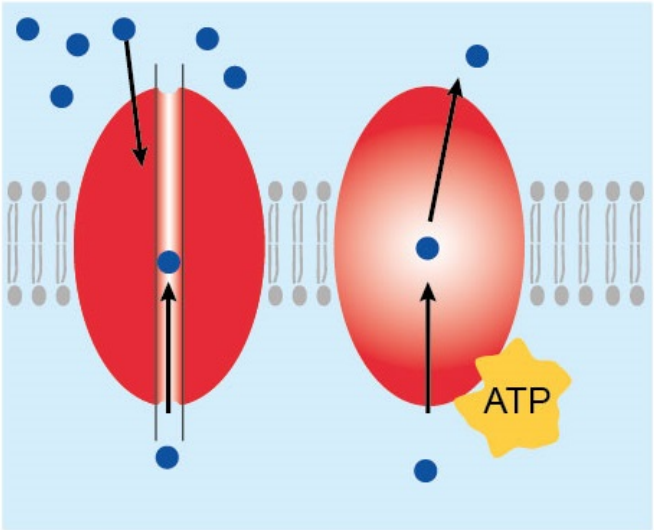


Figure 2.3 Diagram of active transport

PINOCYTOSIS

Fluids or particles are engulfed by a cell. The cell membrane invaginates, encloses the fluid or particles, then fuses again, forming a vesicle that later detaches and moves to the cell interior (fig. 2.4). This mechanism also requires energy expenditure. Pinocytosis probably plays a minor role in drug transport, except for protein drugs.

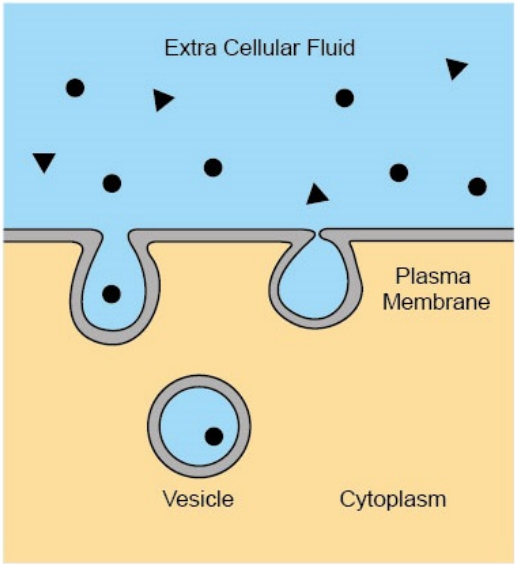


Figure 2.4 Pinocytosis

PHARMACOKINETICS

ABSORPTION

Absorption into blood is influenced by route of administration. Intravenous injection and intramuscular injection bypass the absorption process, but other routes will not. Absorption is dependent on area for absorption and concentration gradient, as well as the route of administration e.g. oral, inhalational, topical / transdermal, buccal, rectal/ vaginal.

Bioavailability is the rate at which an administered dose reaches circulation i.e. the fraction of unchanged drug reaching systemic circulation, following administration by any route. This value is unity (1) for the intravenous route. Bioavailability is dependent on the drug formulation of the active drug. Tables of drug formulation bioavailabilities are available for reference.

Absorption is the transfer of an agent into bloodstream for action on specific receptors (except if local action is required), e.g. Eye drops instilled into conjunctival sac are absorbed by conjunctival vasculature/cornea.

- pH of tears is 7.4
- Tear layer volume is 8-10 micro µm
- Total tear volume 30 micro µm
- One drop medication contains 50 micro µm

Absorption occurs both in corneal epithelium and conjunctival epithelium. Drug crosses epithelial barriers into aqueous humour and then iris tissue and ciliary body. Unless cornea is compromised, only very small amounts of drug actually enter eye. Drug entering eye enters systemic circulation due to aqueous humour flow.

In normal lens containing eye, there is no diffusion into vitreous. If cataract surgery has been done, drugs can diffuse but no clinical consequences.

DISTRIBUTION

Depending on the physical characteristics of the drug administered (e.g. lipophilic), it may be distributed in different physical compartments of the body.

Total body water (0.6L/ Kg)
Cerebrospinal Fluid(CSF)- 500ml
Blood volume (7L)
Blood Plasma (3L)
Total volume of body compartments (40L)

> Drug enters systemic circulation and is distributed to body tissues. Uneven distribution takes place due to differences in blood perfusion, tissue binding and regional pH.
>
> These compartments, since they constitute real physical entities, may be considered real volumes of potential distribution (e.g. plasma volume =3 Litres, Total blood volume= 10 Litres).
>
> Volume of Distribution (V_d) is the term used to describe how the drug is distributed throughout the body. It is the ratio of the amount of drug in the body to the concentration of drug (C) in blood or plasma: V_d = Amount of drug in body / C
>
> Volume of distribution is defined in terms of blood/ plasma concentrations and reflects the apparent space available in both the general circulation and the tissues of distribution. Most important factors governing drug distribution are protein binding, blood flow, membrane permeation and tissue solubility.

Drugs are not simply dissolved in these compartments but bound to cell surfaces and membranes. Inert binding sites are not available for receptor action. However these may be displaced which causes toxic effects.

> After absorption, the drug will enter or pass through various body fluid compartments. If absorbed into the blood stream, it passes through plasma, interstitial fluids and cellular fluids. There, binding to plasma proteins occur. Binding is reversible and it limits absorption. Only the unbound portion is active.
>
> Binding sites on large molecules (not receptors) are referred to as inert binding sites as opposed to receptor binding sites (no pharmacological response). Drug at inert binding sites is in equilibrium with free drug and so alterations in free drug will affect drug concentration, the resultant of which bound drug can be displaced (agents competing for binding site). Interstitial fluids are one of the components of extracellular fluids other than plasma.

METABOLISM

Drug metabolism involves the alteration of the chemical structure of the drug by enzyme systems.

The process involves breaking down the drug to allow it to be used by the body, and converting it to water soluble particles to allow excretion. and it requires enzymes e.g. cytochrome p-450, cytochrome p450 reductase, NADPH and molecular O_2. Non-polar lipophilic agents are biotransformed into their water soluble polar form to be excreted in urine.

For most drugs, metabolism takes place primarily in the liver, although other organ systems can be involved (e.g. lungs, kidneys, GIT, placenta), catalysed primarily by microsomal and in some cases non-microsomal enzyme systems (liver enzymes).

Microsome Activity

Most metabolisms take place on smooth microsomes of liver cells:

- Microsomes contain enzymes involved in metabolism.
- Microsome is a small vesicle that is derived from endoplasmic reticulum (e.g. from broken down liver tissue).
- Microsomes contain the cell's cytochrome P450 (CYP) enzymes, involved in oxidative metabolism.

Ribosome Activity

Ribosome activity can be broken down into two phases:

Phase 1: The alteration of the chemical structure of the drug by enzyme systems (oxidation/ reduction/ hydrolysis) (add O_2/remove O_2/add water) to convert lipophilic agent into a water-soluble polarised form.

Phase 2: Conjugation/ synthetic reactions where large chemical groups (ionised groups) are attached to the molecule, increasing water solubility. This facilitates excretion as well as decreasing pharmacological activity.

These processes require various ribosomal enzymes e.g. cytochrome p450. Microsomal drug oxidations require cytochrome p450, cytochrome p450 reductase, NADPH and O_2. Some drugs undergo either phase 1 or 2. Cytochrome p450 is the most important enzyme, as it catalyses the oxidation of many drugs. Conjunction occurs in liver microsomal enzyme system. Chloramphenicol is metabolized this way.

Cytochrome p450

Cytochrome p450 is a large diverse group of enzymes. Four families of cytochrome p450 have been identified as important in drug metabolism:

- P450 1
- P450 2- largest and most diverse group (p450 2B- one of the most important)
- P450 3- Most important is p450 3A4 (antifungals/anti depressants metabolism etc.)
- P450 4

The activity of these enzymes may be influenced by the action of certain drugs, which act as enzyme inducers. Drug substrates on repeated administration can induce cyctochrome p450 by enhancing the rate of synthesis or reducing rate of degradation, hence causing an acceleration of metabolism.

Other drugs can inhibit cytochrome p450 and hence reduce the metabolism of itself and other concurrently administered agents.

DRUGS AFFECTING CYTOCHROME P450

Enzyme inducers enhances rate of synthesis causing acceleration of metabolism and usually decrease in pharmacological action of inducer and co-administered drugs, e.g. Rifampicin/Alcohol/cigarettes/ phenobarbitone/phenytoin/ carbamazepine/St John's Wort.

For an example of a weakening effect of co-administered drug: St John's Wort weakens effect of antihistamine.

CYTOCHROME P450 ENZYME INHIBITORS

Drug binds to active site and either destroys or reduces the synthesis of the enzyme or reduces the co-factor availability. Co-factors bind to enzyme to maximise activity. Many drugs may increase or decrease the activity of various CYP isozymes by either inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. For example, if one drug inhibits the CYP-mediated metabolism of another drug, the second drug may accumulate within the body to toxic levels, possibly causing an overdose.

Co-factors: These proteins are commonly enzymes and can be considered 'helper molecules' that assist in biochemical transformations.

- Drug binds active site/catalytic site on p450
- Destruction of enzyme
- Reduced synthesis of enzyme
- Reduction in availability of co-factors

E.g. Cimetidine (treatment of peptic ulcers)/ Erythromycin (antibiotic)

May allow toxic metabolite to accumulate/ prolong drug action/increase drug effect to lethal limits

ELIMINATION

It involves the removal of biotransformation products from metabolism. The major organs for drug excretion are the kidneys, liver, GIT, sweat and breast milk.

- Kidneys – Glomerular filtration (passive)
- Kidneys – Tubular secretion
- Kidneys – Tubular reabsorption
- Liver – metabolites may be secreted in bile if sufficiently polar. Some drugs however undergo entero-hepatic circulation.
- Gastro – intestinal tract- passive diffusion of weakly basic drugs
- Lungs – excretion of gaseous anaesthetics

> **Glomerular filtration rate** (**GFR**) describes the flow rate of filtered fluid through the kidney. Glomerular filtration occurs from glomerular capillaries into Bowman's capsules and then to kidney tubules.

- G – Diffusion of substances across the wall of the glomerular capillaries into renal tubule
- TS – As fluid moves along tubule gains other substances from tubule cells and blood capillaries (waste and excess products)
- TR – Useful material are returned to blood including water

> Entero-hepatic refers to the circulation of bile from the liver, where it is produced, to the small intestine, where it aids in digestion of fats and other substances, back to the liver. Drugs eliminated in bile are available for reabsorption into GIT. Concentration may build up and can become toxic.

PHARMACODYNAMICS

How **drugs** exert their effect on the body to produce a therapeutic effect:

- They usually act on physiological processes in body
- They usually combine with a specific molecule (usually temporarily and in a reversible manner)

Disease occurs when there is a departure from the normal physiological processes in the body. Drug will counteract these changes and return the body to a homeostatic state.

Molecular targets for drugs are usually enzymes and associated compounds (from coenzymes to complex receptors on cell membranes, in cells and on DNA). These receptors are responsible for normal physiological control of the body.

Receptors are stimulated:

- Directly
  - Through the nervous system or
  - Through the production of neurotransmitters (a chemical that helps to induce a neural response), or
- Indirectly
  - By the endocrine system through the production of hormones which travel in blood to the receptor site

MODES OF DRUG ACTION

Drugs Working by Chemical Action

- Act on chemical processes in the body
- Direct chemical action

E.g. Magnesium hydroxide is a component of many antacid preparations and is used to neutralise stomach acid.

Drugs Working by Physical Action

E.g. saline solution 0.9% moves through body by osmosis

Drugs Working by Physio-chemical Action

For example, inhalation anaesthetics

- Act by altering the lipid part of cell membranes, especially brain tissue.
- Change in movement of Na+ and K+ ions causing a change in nerve cell responsiveness leading to a loss of consciousness.

Drugs Acting on Enzymes

Enzymes are

- Biological catalysts
- Reversible
- Equilibrium

- May be specific for a substrate

> Many reactions in the body rely on enzymes to catalyse the reactions. A catalyst is involved in a reaction but is unchanged at the end. Equilibrium reactions means that forwards and backwards reactions occur at same rate. Lock and key mechanism specificity, i.e. enzymes will only catalyse specific reactions.

Enzymes may work in several different ways. They usually catalyse reactions in the body. A normal substrate is an endogenous substance that may be similar to the drug. Because the enzyme does not know what to do with the similar structure it discards it to look for a correct substrate. If many more inhibitor molecules are present, this will prevent the reaction occurring.

- **Competitive inhibition –**
  - When the enzyme combines with a substrate (drug) with a very similar structure to the normal substrate
- **Non-competitive inhibition –**
  - Non-competitive inhibitors are not similar to substrate but bind to enzyme usually irreversibly
  - Changes structure of enzyme and renders inactive.

Drugs Acting on Receptors

- Many processes in the body are controlled by a range of molecules including hormones and neurotransmitters
- These chemicals bind to receptors on cell membrane or in cell's cytoplasm or nucleus
- Correct binding will cause a specific action

DRUG RECEPTORS

Most identified drug receptors have been found to be proteins-polypeptide structures that provide necessary diversity and specificity of shape and charge.

Provides two functions:

- Specific recognition of a drug
- Initiation of a biochemical event that leads to characteristic cell response.

Agonists and Antagonists

Agonist and antagonist – opposite effects

When a drug acts as an antagonist, it stops the natural chemical from binding. Competition occurs between natural substrate and the drug.

- Substrates that bind to receptors are known as ligands
- When a drug binds to a receptor and stimulates an action – agonist
- When a drug binds to a receptor and block any action – antagonist

AGONISTS

An agonist is a drug which binds to a drug-receptor and activates it, producing a pharmacological response i.e. contraction/ relaxation/ secretion/ enzyme activation etc.

The response is similar to that elicited by the natural local transmitter or hormone. It is said to have affinity, (ability to combine with other drugs) and efficacy (produces a response from a membrane). Agonists have a stimulation type response. Agonists very closely mimic neurotransmitters.

ANTAGONISTS

Antagonists are drug which weakens the effect of an agonist. They may be:

Competitive Antagonists

It binds reversibly to receptors at the same binding site (active site) as the endogenous agonist. It does not activate the receptor. A bound antagonist will prevent an agonist from binding.

> Antagonist still has affinity but little or no efficacy. Many specific receptors have been identified for opiates, dopamine and insulin. It interacts with the receptor site and blocks or depresses the normal response for that receptor and cannot produce an effect. It blocks the site, preventing other agonists or normal neurotransmitters from interacting.

There is competition between the natural substrate and the drug. For example, consider acetylcholine at the nerve synapse. It is usually released from one nerve synapse to pass across a synaptic cleft to bind to receptors on the next nerve or effector cells to stimulate an action potential. Atropine will bind to the acetylcholine receptors and block the transmission of the nerve impulse. It is a cholinergic antagonist.

> The more the drug is present, the less is the chance of natural substance causing an effect. Effect of atropine could be overcome by more acetylcholine. E.g. If ACH is in excess, an impulse will be generated.

Partial agonist

- Act like the natural stimulus but to a lesser extent
- May not fit exactly to receptor site but will still cause some response
- Reduced response achieved

Mixed agonist/antagonist drugs

- Action depends on receptor
- Act as an agonist at one receptor and antagonist at another

Characteristics:

- Affinity – extent of binding at a receptor site, e.g. the greater the drugs affinity the more likely that binding will occur
- Specificity – ability of a drug to produce an action at a specific site
- Efficacy – ability of a drug to produce an effect at a receptor

E.g. Pilocarpine and atropine

NEUROTRANSMITTERS

A **neurotransmitter** has a specific shape to fit into a receptor site and cause a pharmacological response such as a nerve impulse being sent. The neurotransmitter is similar to a substrate in an enzyme interaction. After attachment to a receptor site, a drug may either initiate a response or prevent a response from occurring. A drug must be a close "mimic" of the neurotransmitter. An **agonist** is a drug that produces a stimulation type response. The agonist is a very close mimic and "fits" with the receptor site and is thus able to initiate a response. An **antagonist** drug interacts with the receptor site and blocks or depresses the normal response for that receptor because it only partially fits the receptor site and cannot produce an effect. However, it does block the site preventing any other agonist or the normal neurotransmitter from interacting with the receptor site (fig. 2.5a).

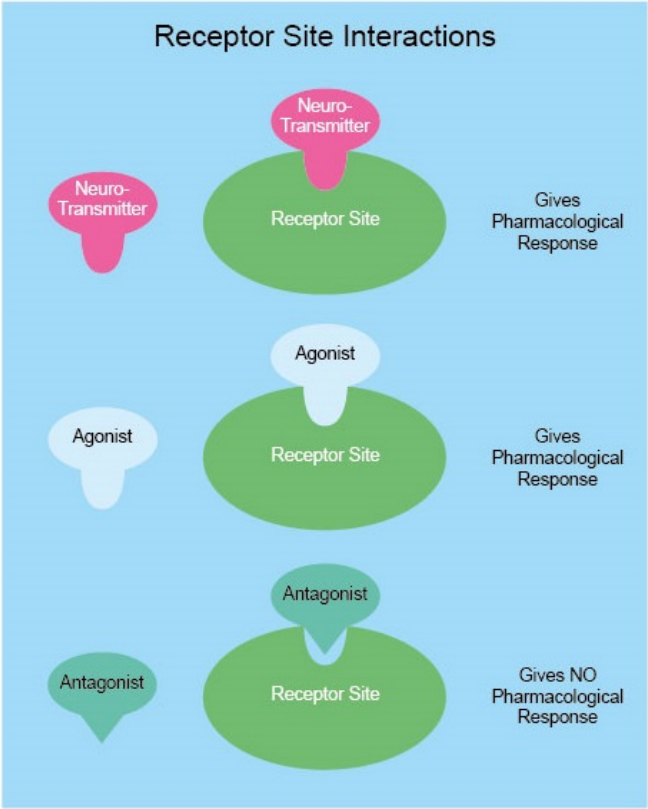


Figure 2.5 (a) Agonist and Antagonist interactions at the receptor site

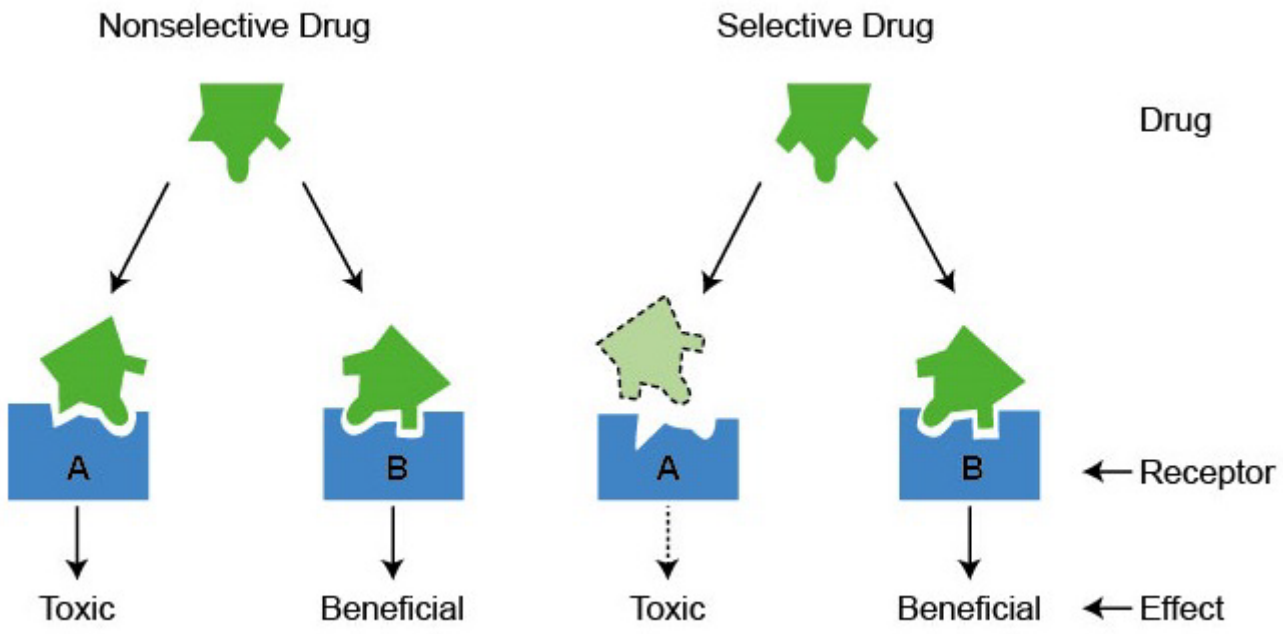


Figure 2.5 (b) Receptor selectivity. A non-selective drug binds equally well to both types of receptor. A selective drug binds with a higher affinity to receptor B rather than receptor A.

Non-competitive antagonists (allosteric) bind to a distinctly separate binding site from the agonist, exerting action on that receptor via the other binding site.

REVERSIBLE DRUG BINDING

- Almost all agonists bind reversibly to the receptor
- Weak chemical bond between drug and receptor
- Agonist dissociates readily from the receptor
- Many antagonists bind reversibly to receptors
- If the agonist concentration is increased it will displace an antagonist from the receptor (competitive)

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