Clinical Pharmacology.

Clinical pharmacology can be described as the application of scientific principles to understanding the ways in which drugs behave and work in humans. A good general understanding of basic pharmacology and how it is applied to the treatment of patients is essential for anyone who prescribes drugs, and is also helpful for those who are directly involved in the management of patients. In order to be able to prescribe drugs appropriately and effectively, prescribers need to appreciate the concepts of how the body handles drugs, i.e. pharmacokinetics, and how these may be altered or influenced. As well as this, we need to know how drugs can exert their effect on the body, and what may alter this potential effect, i.e. pharmacodynamics.

Pharmacokinetics.

Pharmacokinetics can be described as what the body does to the drug over a period of time. The essential principles relate to: absorption, distribution, metabolism and excretion (ADME) together with the route and dose of drug administered.

Drugs may act locally or systemically. Locally means that the drug's effects are confined to a specific area. Systemically means that a drug has to enter the circulation in order to be delivered to its site of action. Drugs may be administered to a patient in many ways;

- Orally – capsule, tablet
- Transdermally - patches
- Sublingually – spray, tablet
- Parentally (injection) – IV, IM, IT, epidural, etc
- Implants – IUD
- Topically – cream, inhaler
- Rectally - suppositories

Bioavailability.

The method of delivery influences the amount of drug reaching the circulation, intended site of action and ultimately, the effect of that drug. 'Bioavailability' is the term used to explain what proportion of an administered dose will reach the circulation unaltered, and therefore be able to have an effect. For example, a drug given intravenously has a bioavailability of 1.0, as 100% of the dose is administered directly into the circulation, and avoids the problems relating to absorption and distribution. A drug given by the oral route will have a reduced bioavailability due to the effects of ADME. The chosen route of administration will depend on many factors including, the condition to be treated, the speed of required drug action, patient preference and available methods of delivery. The main aim is to select the most appropriate route of administration that will be both clinically useful and cost-effective.

ADME – Absorption, Distribution, Metabolism, Excretion.

Absorption.

The process of absorption brings the drug from its site of action into the body's general circulation. Except for those administered intra-venously, all drugs must be absorbed before they can exert their effect. Drugs that exert their effect systemically must cross at least one cell in order to reach the circulation. Most drugs do this by passive diffusion (i.e. movement from an area of high concentration to an area of low concentration) for example, in crossing through the wall of the small intestine where there is high concentration, into the blood stream where there is low concentration. However, some drugs require special transport mechanisms in order to cross cell membranes. These 'active transport' mechanisms are not very important for the absorption of other drugs but are essential in ensuring maintenance of cellular function by transport of ions for example potassium, sugars and amino acids across cell walls.

The rate and extent of drug absorption across a cell membrane will be determined by a number of factors.

1. Surface area for absorption - The larger the surface area available for absorption, the quicker the process will occur. The small intestine has a very large surface area for drug absorption to take place, due to the very large number of villi, coupled with a very rich blood supply. If a patient has a condition that reduces the potential area for drug absorption then the relative absorption of a drug will be reduced, thus interfering with the amount of drug available in the circulation - because of this the final effect of that drug may be altered.

2. Lipid solubility - The lipid solubility of a drug will determine how easily it will pass across a cell membrane. Cell membranes are composed of a double layer of phospholipids and so lipid soluble drugs (or lipophilic drugs) will pass though cell membranes more easily than water-soluble drugs. Another important factor is the state of ionisation of a drug, as only un-ionised drug is lipid soluble. Therefore, the more lipid soluble a drug, the easier it is for that drug to be absorbed from the small intestine after oral administration. This property is used in the design and manufacture of drugs. For example, if a manufacturer wanted to formulate a drug to act directly within the gut, they would look to develop a water-soluble (or low lipidsoluble) drug, so that the drug is held within the gut and not absorbed from the small intestine.

3. First pass metabolism - Some drugs when given orally are absorbed from the small intestine directly into the hepatic portal vein and to the liver. As the liver is the main organ for metabolism, these drugs are then metabolised either partially or fully. This means that the amount of drug entering the circulation is either reduced or completely negated. This effect is known as *first pass metabolism*. Some drugs when taken orally are almost totally inactivated via the first pass metabolism effect and are therefore administered by another route. A good example of this is glyceryl trinitrate, administered sublingually. Other drugs may still be active even after first pass

metabolism if their metabolites are active – propranolol (a beta-blocker) is metabolised to produce an active metabolite (4-hydroxypropranolol). This is why it is important to understand the bioavailability of a drug.

4. Gastric motility and emptying - Most absorption takes place in the small intestine. This means that drugs taken orally need to be disintegrated in the stomach and delivered via emptying of the gastric contents into the intestine. Therefore, anything that alters gastric motility and emptying will result in altering the rate of absorption.

The presence of food after a meal will slow gastric emptying. If drugs are taken with food, then their absorption and effect may be delayed. This is why it is important to ensure that drugs are prescribed to be taken either before or some time after a meal. This ensures quicker delivery to the site of absorption and prevents delaying the drug effect. This is why counselling the patient on when to take their drugs is very important. Sometimes drugs are prescribed 'to be taken with food'. This is to lessen side-effects by preventing large concentrations from entering the circulation so that the drug is absorbed in a steadier manner, due to slower gastric emptying. It is also to prevent local side-effects, like irritation of the stomach lining by using the food as a barrier. Additionally, some illnesses or conditions may affect this process. Gastric emptying may be slowed during a migraine attack and therefore, oral analgesics may not act rapidly enough. This can be addressed by giving the drug via another route for example subcutaneous injection or by combining the oral analgesic with a drug to speed up gastric motility. However, the opposite situation may also be beneficial – that of slowing down gastric motility, thereby slowing down absorption.

5. Time - The amount of time that a drug is in contact with the walls of the small intestine will affect its absorption. Anything that alters gut transit time for example, gastroenteritis will affect time for absorption. Conversely, hypomotility of the gastrointestinal tract may result in higher concentrations of drug entering the circulation.

6. Blood flow - Depending on how drugs are administered, the blood flow to the site of administration will affect the rate of absorption. Blood flow to the gut is usually high and this allows for good absorption into the circulation. Some areas of the body have variable blood flow, eg, muscle tissue, and so absorption from intramuscular injection may vary.

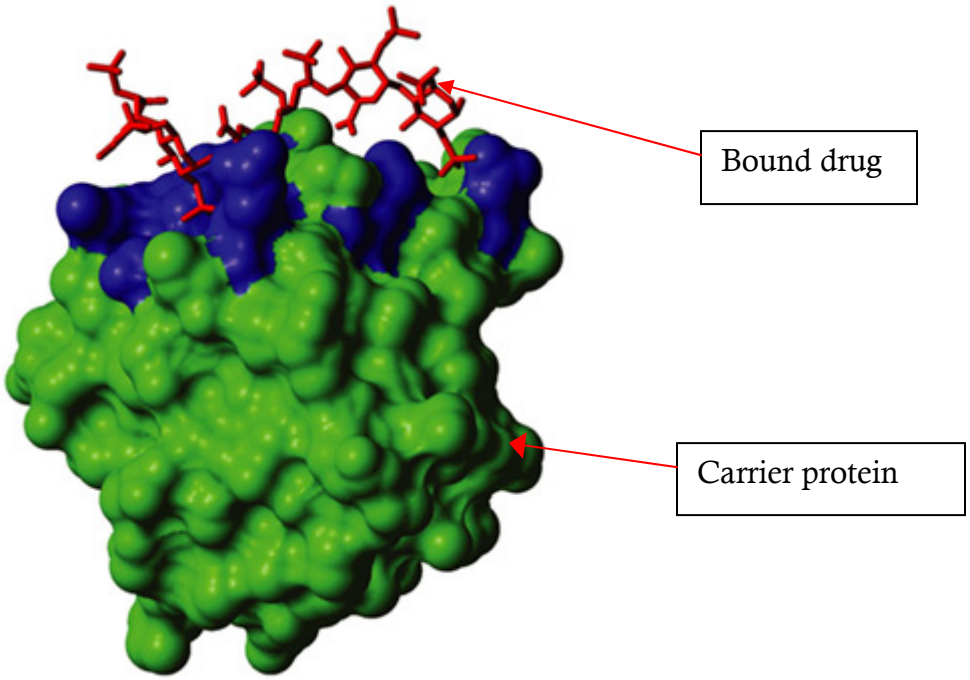
The main point to remember about drug absorption are that drug formulations will affect absorption, and therefore have an impact on the speed and duration of drug action.

Distribution.

Once a drug is absorbed from its site of administration into the circulation it is transported around the body to its site of action. This process is known as distribution. Unless a drug reaches its site of action in an adequate concentration, it will not be able to exert its effect. As with absorption, there are factors that will influence the distribution of drugs around the body.

1. Blood flow - The level of blood supply to tissues will directly affect the distribution of drug to those areas, in turn affecting the rate and extent of drug action at that site. Organs and tissues that receive high blood perfusion (heart, kidneys and brain) will rapidly receive a drug and have a much greater potential of receiving an adequate concentration for the drug to have an effect. Poorly perfused organs and tissues (fat, muscle and bone) may take some time to receive adequate drug concentrations.

2. Protein binding - Most drugs that enter the circulation are not particularly soluble. This means that in order to move around the body via the circulatory system, some proportion of the drug needs a vehicle or carrier. These 'carriers' are usually plasma proteins, and drug molecules are either 'free' in the circulation or 'bound' to these proteins.



It should be noted that only free drug can cross plasma membranes to exert its effect, as drugs bound to plasma proteins are too large to cross the cell membrane. This state of plasma binding can be either reversible or permanent. A drug may enter the circulation and be partially or wholly bound to plasma proteins but over time the drug is released from its protein binding site, or free drug may bind to plasma proteins. This is a dynamic process that allows for equilibrium to be reached between the proportions of bound and free drug.

Albumin is the most abundant plasma protein and generally, drugs that are acidic in nature bind to albumin, whilst drugs that are alkali in nature bind to α_1 -acid glycoprotein. The process of drug binding to plasma protein is a competitive one. This means that if more than one drug that binds to plasma protein is present at the same time in the circulation, these drugs will compete for the plasma protein binding sites.

This is an important concept to understand, particularly for drugs that are highly protein-bound and have a narrow therapeutic index (e.g. warfarin). A narrow

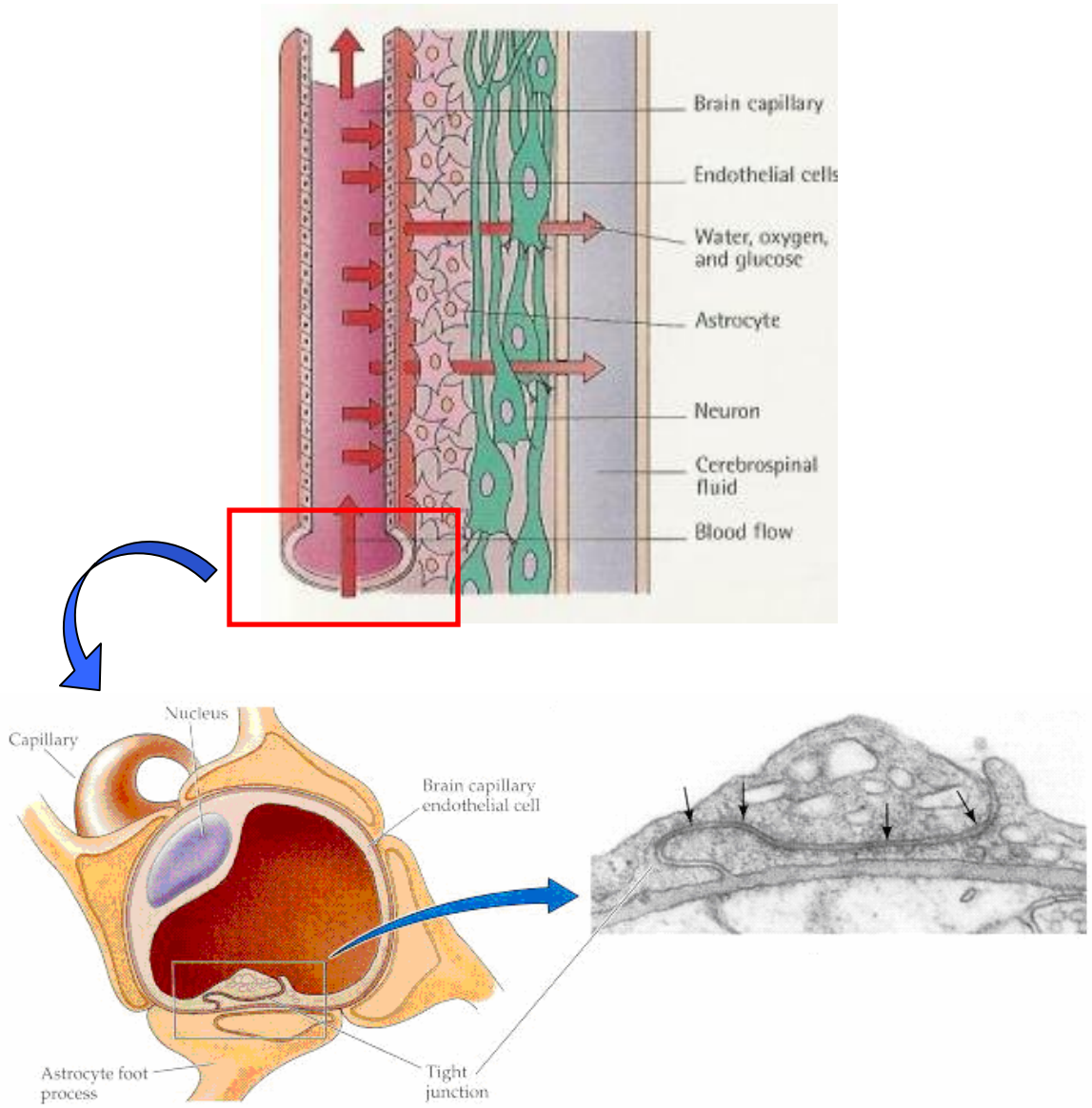
therapeutic index means that the concentration of drug needed to have an effect is very close to that which may be either toxic or ineffective. Using warfarin as an example, if it is competing with other drugs for binding sites, more of it may be displaced from these binding sites and will therefore be free in the circulation, increasing the active amount of drug available. This free drug will eventually be metabolised and excreted. However, if there are any problems with excretion or metabolism, for example poor renal or liver function, then the effect of this free warfarin can be problematic as it may cause the patient to bleed due to higher free plasma concentration exerting a potentially greater effect. Tolbutamide is an example of a drug which competes with, and can displace warfarin from, it's binding sites. Aspirin also competes with warfarin for protein binding sites.

Interactions of this type are more likely to be clinically important in the acute setting such as the administration of loading doses of warfarin before *steady state* is reached. Steady state is where the rate of input of the drug is equal to the rate of elimination, and usually takes a number of doses to achieve. Once a drug has reached steady state then small amounts being displaced from protein binding sites will have less significant effects as metabolism and excretion will deal with these. This is one of the reasons why patients taking warfarin have their International Normalised Ratio (INR) checked regularly and this monitoring is increased when they are started on other drugs known to interact with warfarin, until they are stabilised on the new combination.

This situation could also theoretically arise if a patient is suffering from a disease that alters plasma proteins. In a patient with chronic liver disease (e.g. cirrhosis), drug dosing can be altered to take account of lower albumin concentrations. However, if a patient stabilised on warfarin suddenly develops an acute liver problem, which leads to altered albumin production then drugs that would routinely be bound to albumin may be free in the circulation in higher concentrations than expected and exert a greater than anticipated effect. In patients with reduced hepatic function or disease

states that may impact on plasma protein concentrations, drug doses of highly protein-bound drugs should be reduced.

3. Distribution barriers - Drugs can access and accumulate in certain tissues, or *not* gain access to other tissues due to the existence of barriers. A good example of this is the blood-brain barrier - endothelial cells that only allow highly lipid soluble drugs to cross over into the brain tissue.



A drug that is poorly lipid soluble will have great difficulty in crossing this barrier and will have little or no effect on the brain. However, an anaesthetic agent, which is formulated to be highly lipid soluble, will pass through this barrier. Whilst some of the anaesthetic may pass into other tissues (e.g. muscle or fat stores) the vast majority of the drug will cross the blood-brain barrier and as the brain has a higher blood perfusion than that of muscle or fat, the drug will have the desired effect of rapid anaesthesia. In pregnancy, the placenta forms a barrier between the mother's circulation and that of the fetus. Some drugs which are highly lipophilic can cross this barrier, for example morphine, ethanol, whilst other poorly lipid-soluble molecules cannot easily pass through.

4. Volume of distribution – Once a drug reaches the the general circulation, it can exert its effect by binding to specific receptor sites, or it may bind to other tissues where it has no pharmacological effect, eg, fat stores or certain organs. The term 'volume of distribution' can describe the extent to which a drug is distributed throughout the body and bound to other tissues. Those drugs that are highly distributed throughout body tissues may have a lower plasma concentration and therefore, a higher dose may be required compared to a drug that undergoes little tissue distribution and the majority of which stays within the circulation.

Once a drug has been absorbed and distributed around the body, there must be a mechanism by which excretion of the drug can take place, and this process requires the drug to be metabolised.

Metabolism.

Biotransformation, or drug metabolism, is the process of modifying or altering the chemical composition of the drug. If the property of lipid-solubility makes it easier for a drug to cross cell membranes, it would follow that a further change is required in order to stop any pharmacological activity, and get rid of the drug. To do this, the body tries to make the drug more water soluble (hydrophilic), and less lipid soluble.

Additionally, as un-ionised drugs are more lipid soluble, the body also attempts to ionise the drug so as to reduce lipid-solubility. By ionising the drug there is a reduced chance of it being reabsorbed during it's passage through the kidney, thereby increasing it's chances of being excreted.

Most drug metabolism (but not all) occurs in the liver where a series of enzymes catalyse numerous biochemical reactions. These reactions can be classified into two phases: Phase 1 and Phase 2. Some drugs may undergo both Phase 1 and Phase 2 metabolism, some may undergo only one of these phases and some may undergo Phase 2 before Phase 1. There are also some drugs that are excreted unchanged, without being actively metabolised.

Phase 1 Metabolism – This process results in oxidation, reduction or hydrolysis of a drug. The process of oxidation is the most common and often catalysed by an enzyme from the Cytochrome P450 family (CYP450). Generally, this process makes drugs less effective, but there are some situations where drugs are made more active by this process, a good example being diamorphine (inactive), which when metabolised produces morphine as an active metabolite.

Cytochrome P450 iso-enzymes – Some drugs can increase the rate of synthesis and action of CYP450 enzymes and are known as enzyme inducers (e.g. rifampicin), whilst other drugs can inhibit this process and are known as drug inhibitors (e.g. cimetidine). Generally, induction requires that the CYP450 enzymes are exposed to the enzyme inducer for some time, whilst enzyme inhibitors can exert their effect on the CYP450 system soon after exposure. Sometimes, not only drugs can affect this CYP450 system. Exogenous substances can also affect it and if these substances are taken at the same time as drug therapy, then they can affect the action of the drug. A good example of this is grapefruit juice, which is known to induce the CYP450 system. Patients taking drugs where plasma concentration is crucial due to a narrow therapeutic index e.g. warfarin, cyclosporin, are advised not to drink grapefruit juice, as it can result in speeding up the enzyme system and result in a much reduced

plasma concentration and therapeutic effect of the drug. A full list of enzyme inducers and inhibitors can be found in the British National Formulary (BNF).

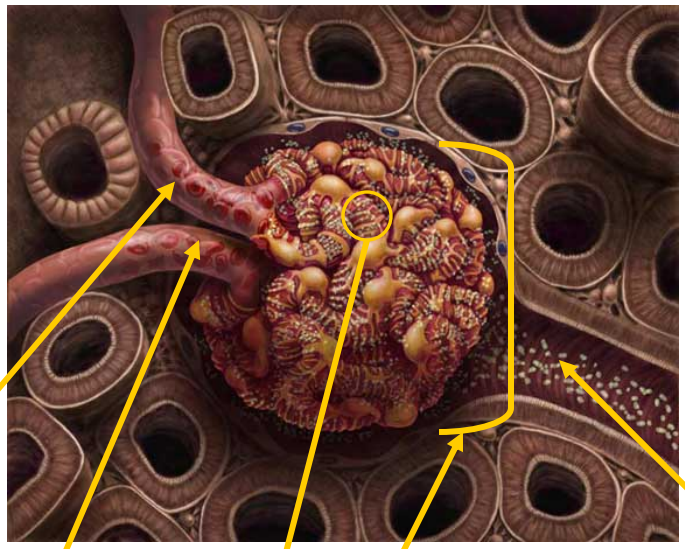
Most drugs are metabolised by concentration-independent mechanisms, i.e. the enzyme responsible for their metabolism is not saturated whilst the drug is within the therapeutic range. There are some enzymes that can be saturated even when the drug is within this therapeutic range. As this happens, small additional doses can lead to a disproportionate rise in plasma concentration and ultimately, to toxicity. An example of this is the drug phenytoin (an antiepileptic). This drug has a narrow therapeutic index and the enzyme responsible for its metabolism becomes saturated within its therapeutic range, so small increases in dose can cause increases in plasma concentrations above the therapeutic level and result in toxicity. As there is great inter-patient variability in this response, phenytoin requires careful dosing and plasma monitoring, until a patient is stable.

Phase 2 Metabolism - Drugs or phase 1 metabolites that are not ionised, or are still active, are made more hydrophilic by the process of conjugation. This process involves the drug or metabolite being attached to an endogenous compound, for example, a glucuronate. The resulting compounds are more readily excreted by the kidneys, as they are more water soluble and polar in nature. As with Phase 1, some drugs are still active after conjugation (e.g. morphine is metabolised to morphine-6-glucuronide), which still exerts an analgesic effect.

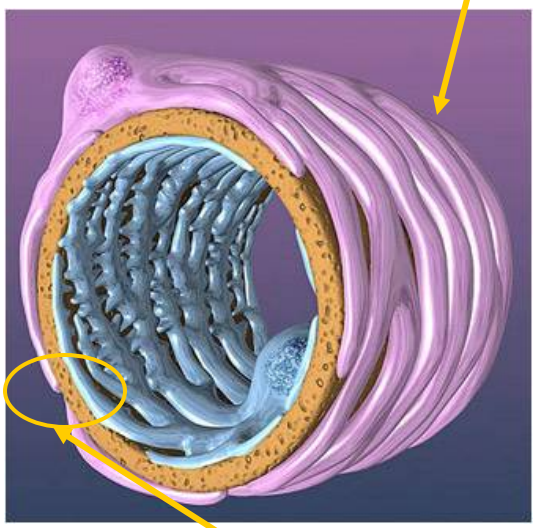
Excretion.

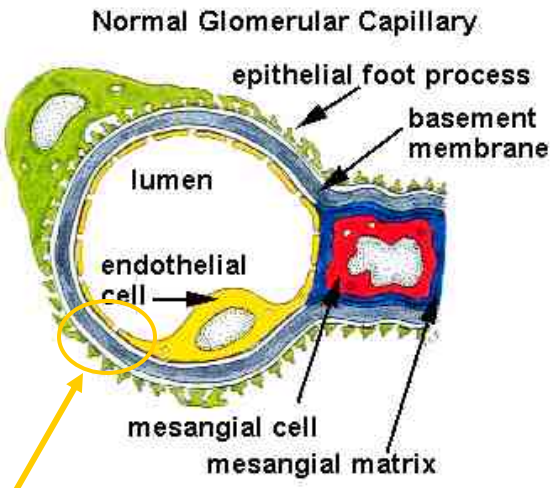
Most drugs (but not all) are excreted via the kidney either unchanged or after the processes of metabolism. The process of drug metabolism may result in a pharmacologically active compound and therefore, the effect of the drug will mainly be dependant on excretion, rather than its metabolism.

Renal excretion - The kidneys have a very good blood supply, receiving around 1.5 litres of blood per minute. Up to one fifth of this is actively filtered by the glomerulus, producing glomelular filtrate. Some drugs or metabolites can pass directly into the kidney at this stage, but they have to be small, whereas larger drugs and those bound to plasma proteins are too large to pass through the filtration system, and are therefore left behind.



Afferent arteriole Efferent arteriole Glomerulus Proximal convoluted tubule

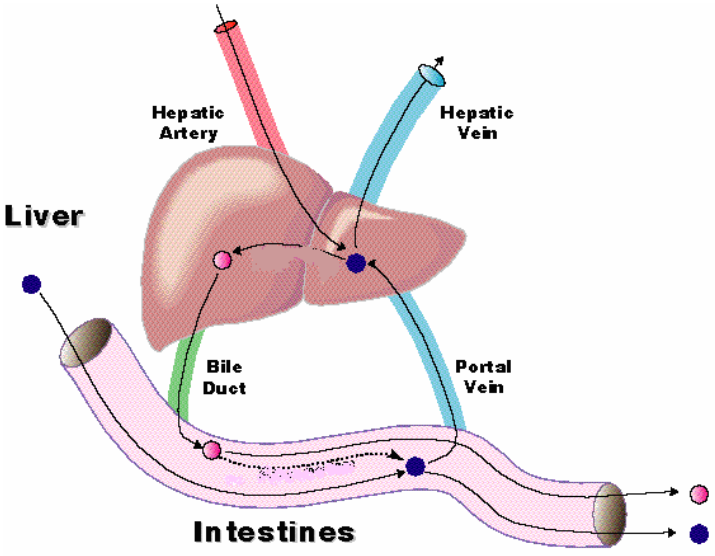




Three-layer filtration unit

Some drugs are actively secreted from the capillaries into the proximal convoluted tubule of the nephron. This process of tubular secretion is an active process requiring carrier systems and energy. It usually involves drugs or metabolites that are strongly acidic or alkali in nature, eg, penicillin. This process can be inhibited by drugs which affect active transport mechanisms (eg probenecid), and in the case of penicillin, this would increase the plasma concentration of penicillin. Some drugs are actively reabsorbed back into the circulation. Active reabsorption enables the body to hold onto vital nutrients and vitamins. Drugs which are still lipid soluble and un-ionised at urine pH can be reabsorbed during this process and continue to exert their effect. Excretion of these drugs can be influenced by altering the pH of urine, e.g. by administering sodium bicarbonate.

Enterohepatic cycling - Other mechanisms of drug excretion include the liver, in the form of bile. Once secreted by the liver into bile, they enter the duodenum via the common bile duct and continue on towards the small intestine. Here, some drugs can be deconjugated by the action of gut bacteria and reabsorbed back into the blood stream from the terminal ileum. They then return to the liver by the enterohepatic circulation (also know as entero-hepatic shunt). The drug undergoes further metabolism and is secreted back into bile and continues going around this process called enterohepatic cycling. Not many drugs are excreted in bile, but those that are and that undergo this cycling mechanism, can have their effect in the body extended.



However, anything that interferes with this mechanism can alter the effect of the drug. A good example of this is the oral contraceptive pill which contains oestrogens that are recycled around the body by this mechanism. If a woman is given a course of broad-spectrum antibiotics, these may alter the gut bacteria and therefore metabolites are not broken down in the small intestine. The oestrogen conjugate is excreted in faeces and enterohepatic cycling is prevented. This can reduce the effect of the oral contraceptive pill. Similarly, diarrhoea can limit the time available for this cycling and also reduce the effect of the pill.

Other methods of excretion - Other methods of excretion include via sweat, breath, tears, saliva and breast milk. These are passive processes and tend to be less important except during breast-feeding.

Half-life - The term half-life ($t_{½}$) describes the time it takes for the plasma concentration of a drug to fall to half its original value and is measured in hours. This is an important factor, as those drugs with very short half-lives (rapidly excreted) will have to be administered very frequently, to ensure adequate plasma concentrations compared to those with longer half-lives, which can be administered at greater intervals.

When a drug is repeatedly given there comes a time when the drug begins to accumulate and a state arises where elimination of the drug by the body matches that being given by the administered dose (steady state). Drugs with short half-lives reach steady state quicker than those with long half-lives. In order to reach steady state with a drug that has a long half-life, a loading dose may be needed to achieve a therapeutic plasma concentration and this is then followed by smaller maintenance doses, to maintain this plasma concentration or steady state.

Summary.

Taking into account the important events of ADME, the prescriber can use this understanding to make some assessments of drug dosing. When a drug is administered the route of administration determines how quickly it will have its effect. The amount of drug in the circulation and its potential effect will depend on how much is administered, whether the drug is plasma protein bound or free, receptor binding properties and how quickly it is metabolised and excreted. The speed at which a drug is managed by the body is one of the key factors in determining the duration of action of that drug. These are the principles of **pharmacokinetics.**

KEY LEARNING POINTS.

1. **Pharmacokinetics relates to how the body deals with a drug.**
2. **The events of this process are absorption, distribution, metabolism, and excretion.**
3. **The formulation of a drug will affect how it is absorbed.**
4. **Distribution of a drug around the body is not uniform.**
5. **Well-perfused tissues receive drugs faster.**
6. **Protein binding is important, and can be affected by systemic disease.**
7. **The Cytochrome P450 system is the main source of phase 1 metabolism**
8. **Metabolism occurs mainly in the liver.**
9. **Phase 2 metabolism makes it easier for the body to get rid of a drug by making is water soluble, and by ionising it.**
10. **The kidney is the most important route of drug excretion.**
11. **Entero-hepatic shunting can be affected by antibiotic therapy and so reduce the effectiveness of certain drugs.**
12. **In the elderly, impairment of renal and hepatic function can impair drug metabolism and excretion.**

Pharmacodynamics

Pharmacodynamics studies the effects that the drug will have on the body at both receptor level and on the body systems as a whole.

The many and varied physiological systems and mechanisms that control all bodily functions are very complex. These functions are monitored and controlled by many different electrical and chemical messenger systems that work together to maintain homeostasis. The body's own endogenous signals that act on receptors are known as *ligands,* eg, insulin, noradrenalin and serotonin are all naturally-occurring substances which act as ligands at receptor sites. Drugs exert their effect by altering to a lesser or greater degree the body's own physiological systems, and in this way drugs act as exogenous ligands. Drugs can act at enzyme systems, ion channels, at carrier mechanisms, or at receptors

Drugs acting at enzyme systems

Some drugs work by altering the effect of the body's enzyme systems. Sometimes, the drug may resemble the enzyme's natural substrate and so competition is set up between the drug and the natural substrate for binding to the enzyme. Other times, the drug may bind irreversibly to the enzyme's active site, therefore rendering it unable to carry out its usual function. An example of a drug acting on an enzyme system is that of the angiotensin converting enzyme inhibitors (ACE inhibitors) which block the enzymatic conversion of inactive angiotensin I to the angiotensin II, which is a powerful vasoconstrictor. These drugs are used to control blood pressure by preventing vasoconstriction, as well as having other indications.

Drugs acting at ion channels

Some systems are controlled by cells allowing the selective movement of certain ions across cell membranes, for example calcium or potassium ions, which sets up an electrical potential gradient across the membrane. Anything that alters this selective movement across a cell membrane can alter this electrical potential and therefore, affect that body system. For example, calcium channel blocker drugs (e.g. nifedipine, diltiazem) act by blocking natural channels across cell membranes, which under certain situations allow the passage of calcium ions across smooth muscle cells. This results in an altered electrical potential and therefore an altered physiological response from the muscle cells, resulting in a reduced force of contraction of smooth muscle in the heart.

Drugs acting on carrier mechanisms

These transport systems are energy-dependant carrier mechanisms and some drugs can interfere with these mechanisms. Examples include digoxin which blocks the hydrogen/potassium pump in the heart, and the proton pump inhibitor drugs such as omeprazole, which block the sodium/potassium pump in the gastric mucosa.

Drugs acting at receptors

Drugs have their effect at receptors by mimicking an endogenous ligand and binding to a receptor site in the same way as one of the body's own signalling molecules, forming a ligand-receptor complex. The receptor sites are usually protein molecules either on the surface of a cell or located intra-cellularly. In order for a drug to act as a ligand at a parlicular receptor site it must have a complementary structure to that site. An analogy frequently used to illustrate this is that of a lock and key mechanism.

Not all drugs bind to their chosen receptors to the same degree. The term *'affinity'* is used to describe the extent to which a drug binds to a receptor. The greater affinity a drug has for a receptor the greater the binding between the drug and its chosen

receptor will be. Some drugs have greater or lesser affinity for their receptors than others.

Whilst drugs may exert an effect at a receptor, the extent and type of this effect will also vary. The effect of the ligand-receptor complex will vary depending on how the drug exerts its effect. In some cases this drug-ligand complex causes a specific response and these types of ligands are called *agonists*. An example of a drug acting as an agonist is salbutamol, a $ß_2$-receptor agonist used in asthma, which binds to receptors on the smooth muscle in the bronchioles causing bronchodilation.

Some ligand-drug complexes do not have an effect but they stop or block a particular natural messenger system from having its effect and this type of ligand is called an *antagonist*. An example of a drug acting as an antagonist is atenolol, a beta-blocker ($ß_1$-adrenoceptor antagonist) used in angina. It is used to block the $ß_1$ effects of adrenaline on the heart, causing a slowing of the force of contraction, reduction in cardiac oxygen consumption and alleviation of angina pain.

Agonists can be described as either complete or partial agonists. A drug is a *complete agonist* if it can exert its maximal effect when all receptors are occupied. If it can only exert a sub-maximal effect (i.e. less than the body's own natural agonist effect) when all receptors are occupied, it is termed a *partial agonist.* The term *efficacy* is used to describe the ability of a drug to exert an effect at a receptor site. We can say that agonists have affinity for, and efficacy at, receptor sites but whilst antagonists have affinity for receptor sites, they do not directly exert an effect and so have no efficacy. The term *potency* is used to describe the relative concentration (or dose) of a drug that has to be present in order to produce the desired effect. The more potent a drug, the less that has to be administered for a given effect.

Antagonists stop or block a system by occupying a receptor site. The body will still be producing its own natural chemical messengers (ligands) but these cannot exert their usual effect at a receptor site in the presence of the antagonist. Antagonists can

be *competitive* or *non-competitive* in nature. A competitive antagonist will compete with the natural ligand for receptor sites and form a reversible bond. As more drug antagonist is made available (e.g. by giving further doses and increasing the plasma concentration of drug) then the antagonist is able to occupy more receptors than the agonist and more of the body's own natural response is blocked. In order to overcome this effect more of the body's own natural agonist needs to be made available in order to compete with the antagonist for these receptor sites, i.e. competition needs to be set up between agonist and antagonist. A non-competitive antagonist also forms a bond at a receptor site but often this bond is almost irreversible. Therefore, no matter how much of the natural agonist is present, the antagonist still exerts its effect.

Receptor Superfamilies.

There are a number of different types of receptor, situated on the cell membrane and also inside the cell. These are:

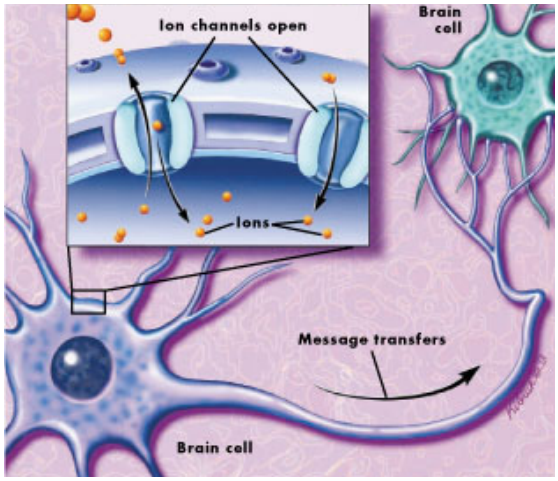
1. ion channels (response in milliseconds), eg, acetyl choline, noreadrenaline
2. G-protein coupled (response in seconds), eg, histamine, prostaglandin
3. tyrosine kinase (response in minutes), eg, insulin, growth factor
4. intracellular receptors, eg, steroids

The first three on this list are all found on the cell membrane, and have a response time ranging from milliseconds to minutes. The intracellular receptors are found on the cell nucleus, and usually affect protein production by interfering with DNA activity, and therefore can have very wide-ranging effects.

Ion-channels

These are pore-forming proteins that help to establish and control the small voltage gradient across the plasma membrane of all living cells by allowing the flow of ions down their electrochemical gradient. They are present in cell membranes and regulate the flow of ions across the membrane in all cells. They are, typically, an assembly of several proteins, usually arranged in a circle, closely packed around a

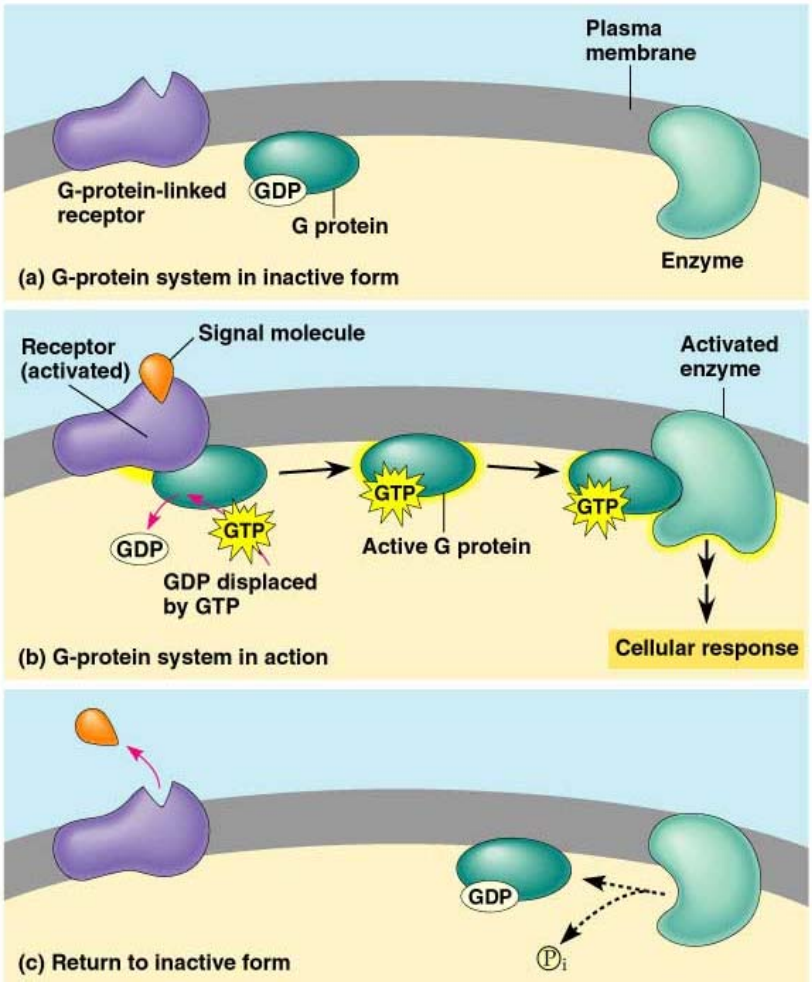
water-filled pore passing through the cell membrane. While some channels permit the passage of ions based solely on charge, the archetypal channel pore is just one or two atoms wide at its narrowest point, and allows only a specific species of ion, such as sodium or potassium, and conveys them through the membrane in single file very quickly.



In some ion channels, passage through the pore is governed by a *'gate'* which may be opened or closed by chemical (ligand) or electrical signals (voltage), temperature, or mechanical force, depending on the variety of channel. Because *'voltage-gated'* channels underlie the nerve impulse and because *'ligand-gated'* channels mediate conduction across the synapses, channels are especially prominent components of the nervous system. The majority of offensive and defensive toxins that organisms have evolved for shutting down the nervous systems of predators and prey (e.g., the venoms produced by spiders, scorpions, snakes, fish, bees, sea snails and others) work by blocking ion channel pores. In addition, ion channels figure in a wide variety of biological processes that involve rapid changes in cells, such as cardiac, skeletal, and smooth muscle contraction, epithelial transport of nutrients and ions, T-cell activation and pancreatic beta-cell insulin release. In the search for new drugs, ion channels are a favorite target. There are four identified types of ion-channel through which calcium, potassium, sodium or chloride ions selectively pass. There are also some 'promiscuous' channels which allow any cation to pass through. The pharmacological properties of all of these channels is yet to be fully established.

G-protein coupled

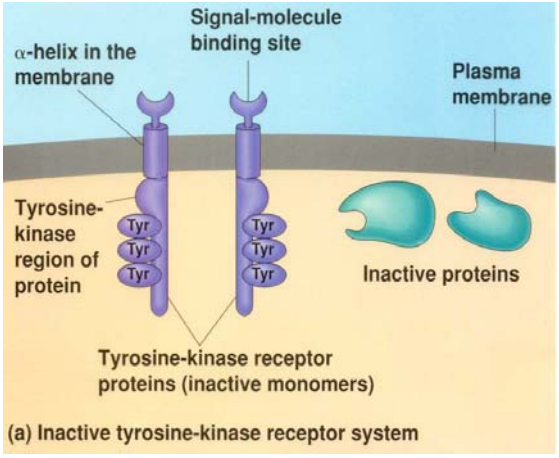
These comprise a large family of transmembrane receptors that activate signal transduction pathways inside the cell, and ultimately bring about cellular responses. G protein-coupled receptors are found only in eukaryotes (multi-celled organisms), including yeast, plants, and animals. The ligands that bind and activate these receptors include light-sensitive compounds, odours, pheromones, hormones, and neurotransmitters, and vary in size from small molecules to large proteins. G protein-coupled receptors are involved in many diseases, but are also the target of around half of all modern medicinal drugs. These receptors are activated by an external signal in the form of a ligand or other signal mediator. This creates a conformational change (shape change) in the receptor, causing activation of a G protein. The subsequent effect depends on the type of G protein involved.

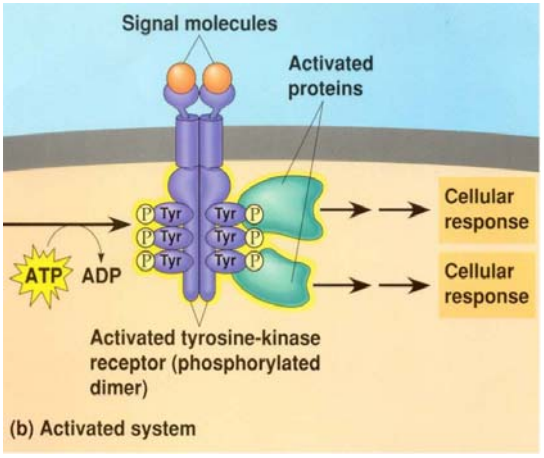


The transduction of the signal through the membrane by the receptor is not completely understood. It is known that the inactive G protein is bound to the receptor in its inactive state. Once the ligand is bound and recognised, the receptor changes shape and it is this which appears to activate the G protein, which detaches from the receptor. The receptor can now either activate another G protein or switch back to its inactive state.

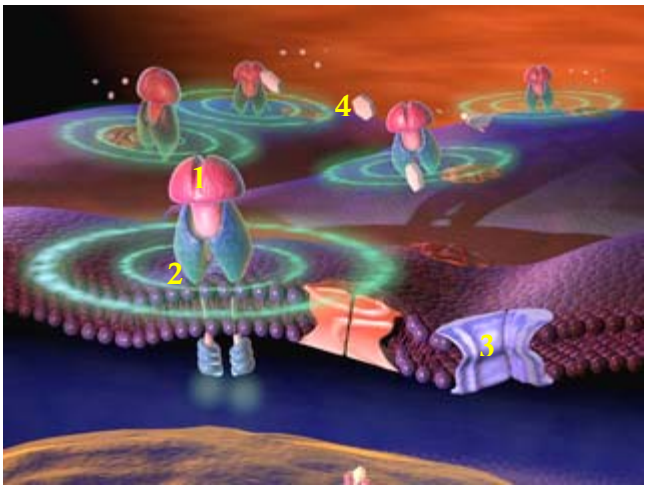
Tyrosine-kinase

These are high-affinity cell surface receptors for many polypeptide growth factors, cytokines and hormones. Receptor tyrosine kinases have been shown to be not only key regulators of normal cellular processes but also to have a critical role in the development and progression of many types of cancer. Tyrosine kinase receptors, including the insulin receptor, mediate their activity by causing the addition of a phosphate group to particular tyrosines on certain proteins within a cell. This then mediates a cellular response.





In the case of the insulin receptor (diagram to the right), the binding of insulin (1) to the kinase receptor (2) leads to an increase in availability of glucose -transport-protein-4 (GLUT4) (3). These transport proteins in the cell surface allow the movement of glucose (4) into the cell, increasing the uptake of glucose from blood into these tissues.

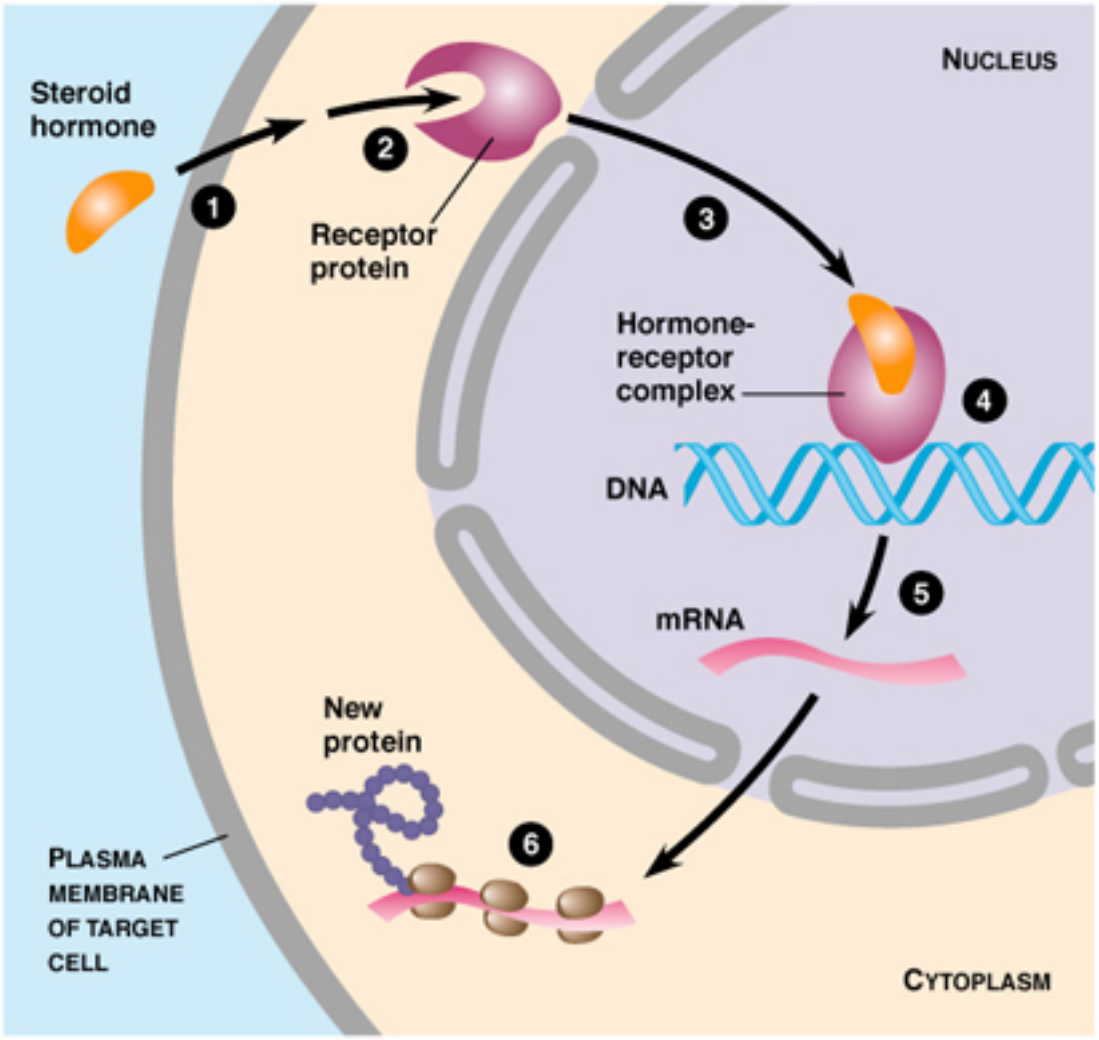


Intra-cellular receptors

These are located inside the cell rather than on the cell membrane, such as the nucleus or the endoplasmic reticulum. The ligands that bind to them are usually intracellular second messengers like inositol trisphosphate (IP_3), and extracellular lipophilic hormones like steroid hormones. There is also some evidence that certain steroid hormone receptors can extend through cell membranes at the surface of cells and might be able to interact with hormones that remain outside of cells. Free steroids enter the cell cytoplasm and interact with their receptor.

In this process heat-shock protein is dissociated, and the activated receptor-ligand complex is translocated (moved) into the nucleus. After binding to the ligand, steroid receptors often form a complex. In the nucleus the complex acts as a transcription factor, augmenting or suppressing transcription of particular genes by its action on DNA. As a result messenger RNA is produced that exits the nucleus and interacts with ribosomes. There, after translation of the genetic message, specific proteins are produced. In this way, steroid hormones or drugs which bind with steroid hormone receptors, can bring about changes in protein production within the body, thereby

affecting major body systems and processes.



Summary.

The concepts of pharmacokinetics and pharmacodynamics are very complex, and it is important that prescribers and health care professionals directly involved in patient care have at least a basic understanding of these in order to be able to understand drug therapy. They are also important in understanding how drugs interact and why drugs can exert unwanted or adverse effects.

KEY LEARNING POINTS.

1. **Regulation of cellular activity is achieved by continuous inter-cell signaling.**
2. **The signaling is by molecules acting on receptors on the cell surface, or inside the cell.**
3. **Activation of a receptor site by a ligand brings about metabolic or ionic change within a cell.**
4. **Many drugs either block or stimulate the receptor.**
5. **Ion channels control in influx and efflux of specific ions, affecting the electrical charge of a cell.**
6. **G-protein coupled receptors rely on the activation of an intra-cellular protein to activate a change.**
7. **Tyrosine kinase receptors are essential in the processes of growth regulation and hormonal control.**
8. **Steroid receptors are located within the cell.**
9. **Activation of steroid receptors leads to a change in DNA activity, and therefore altered transcription of proteins.**