What is pharmacology?

Pharmacology is the study of the actions, mechanisms, uses and adverse effects of drugs.

A drug is any natural or synthetic substance that alters the physiological state of a living organism. Drugs can be divided into two groups:

- Medicinal drugs: substances used for the prevention, treatment and diagnosis of disease.
- Nonmedicinal (social) drugs: substances used for recreational purposes. These drugs include illegal substances such as cannabis, heroin and cocaine, as well as everyday substances such as caffeine, nicotine and alcohol (see Chapter 9).

Although drugs may have a selective action, there is always a risk of adverse effects associated with the use of any drug, and the prescriber should assess the balance of desired and adverse effects when deciding which drug to prescribe.

Drug names and classification

A single drug can have a variety of names and belong to many classes. Drugs are classified according to their:

- Pharmacotherapeutic actions
- Pharmacological actions
- Molecular actions
- Chemical nature

When a drug company’s patent expires, the marketing of the drug is open to other manufacturers. Although the generic name is retained, the brand names can be changed.

How do drugs work?

Most drugs produce their effects by targeting specific cellular macromolecules, often proteins. The majority act as receptors in cell membranes, but they can also inhibit enzymes and transporter molecules. Some drugs directly interact with molecular targets found in pathogens. For example, β-lactam antibiotics are bactericidal, acting by interfering with bacterial cell wall synthesis.

Certain drugs do not have conventional targets. For example, succimer is a chelating drug that is used to treat heavy metal poisoning. It binds to metals, rendering them inactive and more readily excretable. Such drugs work by means of their physicochemical properties and are said to have a nonspecific mechanism of action. For this reason, these drugs must be given in much higher doses than the more specific drugs. Another example would be antacids used to reduce the effect of excessive acid secretion in the stomach.

Transport systems

Ion channels

Ion channels are proteins that form pores in the cell membrane and allow selective transfer of ions (charged species) in and out of the cell. Opening or closing of these channels is known as gating; this occurs as a result of the ion channel undergoing a change in shape. Gating is controlled either by a neurotransmitter (receptor operated channels) or by the membrane potential (voltage-operated channels).

Some drugs modulate ion channel function directly by blocking the pore (e.g. the blocking action of local anaesthetics on sodium channels); others bind to a part of the ion channel protein to modify its action (e.g. anxiolytics acting on the γ-aminobutyric acid [GABA] channel). Other drugs interact with ion channels indirectly via a G-protein and other intermediates.

Carrier molecules

Carrier molecules located in the cell membrane facilitate the transfer of ions and molecules against their concentration gradients. There are two types of carrier molecule.

1. Energy-independent carriers: These are transporters (move one type of ion/molecule in one direction), symporters (move two or more ions/molecules) or antiporters (exchange one or more ions/molecules for one or more other ions/molecules).
2. Energy-dependent carriers: These are termed pumps (e.g. the Na⁺/K⁺ adenosine triphosphatase [ATPase] pump).

Enzymes

Enzymes are protein catalysts that increase the rate of specific chemical reactions without undergoing any net change themselves during the reaction. All enzymes are potential targets for drugs. Drugs either act as a false substrate for the enzyme or inhibit the enzyme’s activity directly, usually by binding the catalytic site on the enzyme (Fig. 1.1).

Certain drugs may require enzymatic modification. This degradation converts a drug from its inactive form (prod-rug) to its active form.
Receptors

Receptors are the means through which endogenous ligands produce their effects on cells. A receptor is a specific protein molecule usually located in the cell membrane, although intracellular receptors and intranuclear receptors also exist. A ligand that binds and activates a receptor is an agonist. However, a ligand that binds to a receptor but does not activate the receptor and prevents an agonist from doing so is called an antagonist.

The following are naturally occurring ligands.

- **Neurotransmitters**: Chemicals released from nerve terminals that diffuse across the synaptic cleft, and bind to presynaptic or postsynaptic receptors.
- **Hormones**: Chemicals that, after being released locally, or into the bloodstream from specialized cells, can act at neighbouring or distant cells.

Each cell expresses only certain receptors, depending on the function of the cell. Receptor number and responsiveness to external ligands can be modulated.

In many cases, there is more than one receptor for each messenger so that the messenger often has different pharmacological specificity and different functions according to where it binds (e.g. adrenaline is able to produce different effects in different tissues because different adrenergic receptors are formed of different cell types).

There are four main types of receptor (Table 1.1).

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**Table 1.1** The four main types of receptor and their uses

<table>
<thead>
<tr>
<th>Receptor type</th>
<th>Time for effect</th>
<th>Receptor example</th>
<th>Function example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ion channel–linked</td>
<td>Milliseconds</td>
<td>Nicotinic acetylcholine receptor</td>
<td>Removing hand from hot water</td>
</tr>
<tr>
<td>G-protein–linked</td>
<td>Seconds</td>
<td>β-Adrenergic receptor</td>
<td>Airway smooth muscle relaxation</td>
</tr>
<tr>
<td>Tyrosine kinase–linked</td>
<td>Minutes</td>
<td>Insulin receptor</td>
<td>Glucose uptake into cells</td>
</tr>
<tr>
<td>DNA-linked</td>
<td>Hours to days</td>
<td>Steroid receptor</td>
<td>Cellular proliferation</td>
</tr>
</tbody>
</table>

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**1. Receptors directly linked to ion channels**

Receptors that are directly linked to ion channels (Fig. 1.2) are mainly involved in fast synaptic neurotransmission. A classic example of a receptor linked directly to an ion channel is the nicotinic acetylcholine receptor (nicAChR).

The nicAChRs possess several characteristics:

- **Acetylcholine** (ACh) must bind to the N-terminal of both α subunits to activate the receptor.
The receptor shows marked similarities with the two other receptors for fast transmission, namely the GABA<sub>A</sub> and glycine receptors.

2. G-protein–linked receptors

G-protein–linked receptors (Fig. 1.3) are involved in relatively fast transduction. G-protein–linked receptors are the predominant receptor type in the body; muscarinic, ACh, adrenergic, dopamine, serotonin and opiate receptors are all examples of G-protein–linked receptors.

Molecular structure of the receptor

Most of the G-protein–linked receptors consist of a single polypeptide chain of 400 to 500 residues and have seven transmembrane-spanning α helices. The third intracellular loop of the receptor is larger than the other loops and interacts with the G-protein.

The ligand-binding domain is buried within the membrane on one or more of the α helical segments.

G-proteins

Fig. 1.4 illustrates the mechanism of G-protein–linked receptors.

- In resting state, the G-protein is unattached to the receptor and is a trimer consisting of α, β and γ subunits (see Fig. 1.4A).
- The occupation of the receptor by an agonist produces a conformational change, causing its affinity for the trimer to increase. Subsequent association of the trimer with the receptor results in the dissociation of bound guanosine diphosphate (GDP) from the α subunit.
Guanosine triphosphate (GTP) replaces GDP in the cleft thereby activating the G-protein and causing the α subunit to dissociate from the βγ dimer (see Fig. 1.4B).

- Alpha-GTP represents the active form of the G-protein (although this is not always the case: in the heart, potassium channels are activated by the βγ dimer and recent research has shown that the γ subunit alone may play a role in activation). This component diffuses in the plane of the membrane where it is free to interact with downstream effectors such as enzymes and ion channels. The βγ dimer remains associated with the membrane owing to its hydrophobicity (see Fig. 1.4C).
- The cycle is completed when the α subunit, which has enzymic activity, hydrolyses the bound GTP to GDP. The GDP-bound α subunit dissociates from the effector and recombines with the βγ dimer (see Fig. 1.4D).

This whole process results in an amplification effect because the binding of an agonist to the receptor can cause the activation of numerous G-proteins, which in turn can each, via their association with the effector, produce many other molecules intracellularly.

Many types of G-protein exist. This is probably attributable to the variability of the α subunit. Gs and Gi/Go cause stimulation and inhibition, respectively, of the target enzyme adenylyl cyclase. This explains why muscarinic ACh receptors (Gs/Gi,–linked) and β-adrenoreceptors (Gs–linked) located in the heart produce opposite effects. The bacterial toxins cholera and pertussis can be used to determine which G-protein is involved in a particular situation. Each has enzymic action on a conjugation reaction with the α subunit, such that:

- Cholera affects Gs causing continued activation of adenylyl cyclase. This explains why infection with cholera toxin results in uncontrolled fluid secretion from the gastrointestinal tract.
- Pertussis affects Gi and Gs, causing continued inactivation of adenylyl cyclase. This explains why infection with Bordetella pertussis causes a “whooping” cough, characteristic of this infection, because the airways are constricted, and the larynx experiences muscular spasms.

**Targets for G-proteins**

G-proteins interact with either ion channels or secondary messengers. G-proteins may activate ion channels directly, for example, muscarinic receptors in the heart are linked to potassium channels which open directly on interaction with the G-protein, causing a slowing down of the heart rate. Secondary messengers are a family of mediating chemicals that transduces the receptor activation into a cellular response. These mediators can be targeted, and three main secondary messenger systems exist as targets of G-proteins (Fig. 1.5).
Adenylyl cyclase/cyclic adenosine monophosphate system—Adenylyl cyclase catalyses the conversion of ATP to cyclic adenosine monophosphate (cAMP) within cells. The cAMP produced causes activation of certain protein kinases, enzymes that phosphorylate serine and threonine amino acid residues in various proteins, thereby producing either activation or inactivation of these proteins. An example of this system can be observed in the activation of β1-adrenergic receptors found in cardiac muscle. The activation of β1-adrenergic receptors results in the activation of cAMP-dependent protein kinase A, which phosphorylates and opens voltage-operated calcium channels. This increases calcium levels in the cells and results in an increased rate and force of contraction. An inhibitory example of this system can be observed in activation of opioid receptors. The receptor linked to the “Gі” protein inhibits adenylyl cyclase and reduces cAMP production.

Phospholipase C/inositol phosphate system—Activation of M1, M3, 5-hydroxytryptamine (5-HT3), peptide and α1-adrenoceptors, via Gαs, cause activation of phospholipase C, a membrane-bound enzyme, which increases the rate of degradation of phosphatidylinositol (4,5) bisphosphate into diacylglycerol (DAG) and inositol (1,4,5) triphosphate (IP3). DAG and IP3 act as second messengers. IP3 binds to the membrane of the endoplasmic reticulum, opening calcium channels and increasing the concentration of calcium within the cell. Increased calcium levels may result in smooth muscle contraction, increased secretion from exocrine glands, increased hormone or transmitter release, or increased force and rate of contraction of the heart. DAG, which remains associated with the membrane owing to its hydrophobicity, causes protein kinase C to move from the cytosol to the membrane where DAG can regulate the activity of the latter. There are at least six types of protein kinase C, with over 50 targets which can lead to:

- release of hormones and neurotransmitters
- smooth muscle contraction
- inflammation
- ion transport
- tumour promotion

Guananyl cyclase system—Guananyl cyclase catalyses the conversion of GTP to cyclic guanosine monophosphate (cGMP). This cGMP goes on to cause activation of protein kinase G which in turn phosphorylates contractile proteins and ion channels. Transmembrane guanylyl cyclase activity is exhibited by the atrial natriuretic peptide receptor upon the binding of atrial natriuretic peptide. Cytoplasmic guanylyl cyclase activity is exhibited when bradykinin activates receptors on the membrane of endothelial cells to generate nitric oxide, which then acts as a second messenger to activate guanylyl cyclase within the cell.

3. Tyrosine kinase-linked receptors
Tyrosine kinase-linked receptors are involved in the regulation of growth and differentiation, and responses to metabolic signals. The response time of enzyme-initiated transduction is slow (minutes). Examples include the receptors for insulin, platelet-derived growth factor and epidermal growth factor.

Activation of tyrosine kinase receptors results in auto-phosphorylation of tyrosine residues leading to the activation of pathways involving protein kinases. These receptors have become important targets for certain types of anticancer drugs (see Chapter 13).

4. Deoxyribonucleic acid–linked receptors
Deoxyribonucleic acid (DNA)–linked receptors are located intracellularly and so agonists must pass through the cell membrane to reach the receptor. The agonist binds to the receptor and this receptor–agonist complex is transported to the nucleus, aided by chaperone proteins. Once in the nucleus, the complex can bind to specific DNA sequences and so alter the expression of specific genes. As a result, transcription of this specific gene to messenger ribonucleic acid (mRNA) is increased or decreased and thus the amount of mRNA available, for translation into a protein, increases or decreases. The process is much slower than for other receptor–ligand interactions, and the effects usually last longer. Examples of molecules with DNA-linked receptors are corticosteroids, thyroid hormone, retinoic acid and vitamin D.

HINTS AND TIPS

Drugs, like naturally occurring chemical mediators, act on receptors located in the cell membrane, in the cytoplasm of the cell, or in the cell nucleus, to bring about a cellular, and eventually organ or tissue, response.

DRUG–RECEPTOR INTERACTIONS

Most drugs produce their effects by acting on specific protein molecules called receptors.

Receptors respond to endogenous chemicals in the body that are either synaptic transmitter substances (e.g. ACh, noradrenaline) or hormones (endocrine, e.g. insulin; or local mediators, e.g. histamine). These chemicals or drugs are classed in two ways.

- **Agonists**: Activate receptors and produce a subsequent response.
- **Antagonists**: Associate with receptors but do not cause activation. Antagonists reduce the chance of transmitters or agonists binding to the receptor and thereby oppose their action by effectively diluting or removing the receptors from the system.

Electrostatic forces initially attract a drug to a receptor. If the shape of the drug corresponds to that of the
binding site of the receptor, then it will be held there temporarily by weak bonds or, in the case of irreversible antagonists, permanently by stronger covalent bonds. It is the number of bonds and goodness of fit between drug and receptor that determines the affinity of the drug for that receptor, such that the greater the number of bonds and the better the goodness of fit, the higher the affinity will be.

The affinity is defined by the dissociation constant, which is given the symbol \( K_d \). The lower the \( K_d \), the higher the affinity. \( K_d \) values in the nanomolar range represent drugs (D) with a high affinity for their receptor (R):

\[
K_a = \frac{k_{+1}}{k_{-1}}
\]

The rate at which the forward reaction occurs depends on the drug concentration \([D]\) and the receptor concentration \([R]\):

\[
\text{Forward rate} = K_{a}[D][R]
\]

The rate at which the backward reaction occurs mainly depends on the interaction between the drug and the receptor \([DR]\):

\[
K_d = K_{-1}/K_{+1}
\]

\( K_a \) is the association constant and is used to quantify affinity. It can be defined as the concentration of drug that produces 50% of the maximum response at equilibrium, in the absence of receptor reserve:

\[
K_a = 1/K_d
\]

Drugs with a high affinity stay bound to their receptor for a relatively long time and are said to have a slow off-rate. This means that at any time the probability that any given receptor will be occupied by the drug is high.

The ability of a drug to combine with one type of receptor is termed specificity. Although no drug is truly specific, most exhibit relatively selective action on one type of receptor.

### Agonists

Agonist (A) binds to the receptor (R) and the chemical energy released on binding induces a conformational change that sets off a chain of biochemical events within the cell, leading to a response \((AR^*)\). The equation for this is:

\[
A + R \underset{\text{(i)}}{\rightarrow} AR \underset{\text{(ii)}}{\rightarrow} AR^*
\]

where: (1) affinity; (2) efficacy.

Partial agonists cannot bring about the same maximum response as full agonists, even if their affinity for the receptor is the same (Fig. 1.6).

The ability of agonists, once bound, to activate receptors is termed efficacy, such that:

- Full agonists have high efficacy and are able to produce a maximum response while occupying only a small percentage of the receptors available.
- Partial agonists have low efficacy and are unable to elicit the maximum response even if they are occupying all the available receptors.

### Antagonists

Antagonists bind to receptors but do not activate them; they do not induce a conformational change and thus have no intrinsic efficacy. However, because antagonists occupy the receptor, they prevent agonists from binding and therefore block their action.

Two types of antagonist exist: competitive and non-competitive.

#### Competitive antagonists

Competitive antagonists bind to receptors reversibly, and effectively produce a dilution of the receptors such that:

- A parallel shift is produced to the right of the agonist dose–response curve (Fig. 1.7).
- The maximum response is not depressed. This reflects the fact that the antagonist’s effect can be overcome by increasing the dose of agonist, that is, the block is surmountable. Increasing the concentration of agonist increases the probability of the agonist taking the place of an antagonist leaving the receptor.

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**Fig. 1.6** Comparison of a partial agonist and a full agonist showing (A) the dose–response curve and (B) the log dose–response curve. (From Neal MJ. *Medical Pharmacology at a Glance*, 6th edition. Wiley-Blackwell, 2009.)
Drug–receptor interactions

The size of the shift in the agonist dose–response curve produced by the antagonist reflects the affinity of the antagonist for the receptor. High-affinity antagonists stay bound to the receptor for a relatively long period of time allowing the agonist little chance to take the antagonist's place.

This concept can be quantified in terms of the dose ratio (known as a Schild plot). The dose ratio is the ratio of the concentration of agonist producing a given response in the presence and absence of a certain concentration of antagonist, for example, a dose ratio of 3 tells us that three times as much agonist was required to produce a given response in the presence of the antagonist than it did in its absence.

Noncompetitive antagonists

Noncompetitive antagonists are also known as irreversible antagonists.

- Noncompetitive antagonists also produce a parallel shift to the right of the agonist dose–response curve (see Fig. 1.7).
- Their presence depresses the maximum response, reflecting the fact that the antagonist's effect cannot be overcome by the addition of greater doses of agonist. At low concentrations, however, a parallel shift may occur without a reduced maximum response. This tells us that not all the receptors need to be occupied to elicit a maximum response because irreversible antagonists effectively remove receptors, there must be a number of spare receptors.

Receptor reserve

Although on a log scale the relation between the concentration of agonist and the response produces a symmetric sigmoid curve, rarely does a 50% response correspond to 50% receptor occupancy. This is because there are spare receptors.

This excess of receptors is known as receptor reserve and serves to sharpen the sensitivity of the cell to small changes in agonist concentration. The low efficacy of partial agonists can be overcome in tissues with a large receptor reserve and in these circumstances, partial agonists may act as full agonists.

Potency

Potency relates to the concentration of a drug needed to elicit a response. The EC_{50}, where EC stands for effective concentration, is a number used to quantify potency. EC_{50} is the concentration of drug required to produce 50% of the maximum response. Thus the lower the EC_{50}, the more potent the drug. For agonists, potency is related to both affinity and efficacy, but for antagonists, only affinity is considered because they have no efficacy (Table 1.2).

Other variables can affect the efficacy of a drug beyond its potency. For example, if a potent drug in vitro is metabolized in the stomach or affected by the pH in the stomach, less would be available to reach the target site. This means that, if given as a tablet, it would be less than the in vitro potency predicted.

- Thus the effectiveness of a drug (Pharmacodynamics: the biological effect of the drug on the body) is influenced by many factors which are covered by the term pharmacokinetics: the way the body affects the drug with time, that is, the factors that determine its absorption, distribution, metabolism and excretion.

### Table 1.2 Key definitions

<table>
<thead>
<tr>
<th>Definition</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affinity</td>
<td>Number of bonds and goodness of fit between drug and receptor.</td>
</tr>
<tr>
<td>Agonist</td>
<td>A ligand that binds and activates a receptor.</td>
</tr>
<tr>
<td>Antagonist</td>
<td>A ligand that binds to but does not activate a receptor. Prevents an agonist from binding.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>The ability of agonists, once bound, to activate receptors.</td>
</tr>
<tr>
<td>Potency</td>
<td>Concentration of a drug needed to elicit a response.</td>
</tr>
</tbody>
</table>

**CLINICAL NOTE**

A 22-year-old man is admitted to hospital with signs of respiratory depression, drowsiness, bradycardia and confusion. His girlfriend tells the medical team that he uses heroin and an overdose is therefore suspected. Heroin acts as an agonist, activating the opioid receptors. Naloxone is a competitive antagonist at those receptors and so is administered as treatment. Minutes later the man’s condition improves, and his respiratory rate returns to normal. Careful titration of the naloxone dose should allow treatment of respiratory depression without provoking acute withdrawal signs.

**Fig. 1.7** Comparison of the log dose–response curves for competitive and noncompetitive (irreversible) antagonists. (From Neal MJ. Medical Pharmacology at a Glance, 6th edition. Wiley-Blackwell, 2009.)
**PHARMACOKINETICS**

Pharmacology can be divided into two disciplines. These are:
Pharmacokinetics and Pharmacodynamics

**Administration**

The drug can be administered by a variety of routes.

**Topical**

Topical drugs are applied where they are needed, giving them the advantage that they do not have to cross any barriers or membranes. This means a higher concentration of the drug in the target tissue, with less drug being absorbed into the systemic circulations and therefore less likelihood of unwanted side effects. Examples include skin ointments; ear, nose or eye drops; and aerosols inhaled in the treatment of asthma.

**Enteral**

Enteral administration means that the drug reaches its target via the gut. This is the least predictable route of administration, owing to potential metabolism by the liver following absorption into the hepatoporal circulation (so called *first pass metabolism*) (Fig. 1.8), chemical breakdown and possible binding to food within the gastrointestinal tract. Drugs must cross several barriers, which may or may not be a problem according to their physicochemical properties, such as charge and size.

- However, most drugs are administered orally unless the drug is unstable, or is rapidly inactivated in the gastrointestinal tract, or if the efficacy of absorption from the gastrointestinal tract is uncertain (e.g. vomiting or diarrhoea).
- In addition, absorption of drugs via the buccal or sublingual route avoids the hepatoporal circulation and is, therefore valuable when administering drugs subject to a high degree of first-pass metabolism (which is unavoidable if taken orally). It is also useful for potent drugs with a nondisagreeable taste, such as sublingual nitroglycerin given to relieve acute attacks of angina.
- Also, administration of drugs rectally, such as in the form of suppositories, means that there is less first-pass metabolism by the liver because the venous return from the lower gastrointestinal tract is less than that from the upper gastrointestinal tract. It has the disadvantage, however, of being inconsistent.

**Parenteral**

Parenteral administration means that the drug is administered in a manner that avoids the gut. The protein drug insulin, for example, is destroyed by the acidity of the stomach and the digestive enzymes within the gut and must, therefore be injected, usually subcutaneously.

Intravenous injection of drugs is sometimes used and has several advantages.

- It is the most direct route of administration. The drug enters the bloodstream directly and thus bypasses absorption barriers.
- A drug is distributed in a large volume and acts rapidly.

*Fig. 1.8 The hepatoporal circulation and arterial supply and venous drainage of liver.*
Pharmacokinetics

For drugs that must be given continuously by infusion, or for drugs that damage tissues, this is an important method of administration.

Alternative parenteral routes of administration include subcutaneous, intramuscular, epidural or intrathecal injections, as well as transdermal patches.

Binding the drug to a vehicle or coadministering a vasoconstrictor, such as adrenaline, to reduce blood flow to the site can decrease the rate of drug absorption from the site of the injection. This approach is commonly used in the administration of local anaesthetics and the presence of adrenaline in proportions of local anaesthetics has the added benefit of reducing bleeding by reducing blood flow when used in dental procedures or when carrying out skin biopsies.

Drug absorption

Bioavailability takes into account both absorption and metabolism and describes the proportion of the drug that passes into the systemic circulation. This will be 100% after an intravenous injection, but following oral administration, it will depend on the physiochemical characterizations of the drug, the individual and the circumstances under which the drug is given.

Drugs must cross membranes to enter cells or to transfer between body compartments; therefore drug absorption will be affected by both physiochemical and physiological factors.

Cell membranes

Cell membranes are composed of lipid bilayers and thus absorption is usually proportional to the lipid solubility of the drug. Unionized molecules (B) are far more soluble than those that are ionized (BH+) and surrounded by a “shell” of water.

\[ B + H^+ \rightleftharpoons BH^+ \]

Size

Small molecular size is another factor that favours absorption. Most drugs are small molecules that are able to diffuse across membranes in their uncharged state.

pH—Because most drugs are either weak bases, weak acids or amphoteric, the pH of the environment in which they dissolve, as well as the pKₐ value of the drug, will be important in determining the fraction in the unionized form that is in solution and able to diffuse across cell membranes (see Fig. 1.9). The pKₐ of a drug is defined as the pH at which 50% of the molecules in solution are in the unionized form, and is characterized by the Henderson–Hasselbalch equation:

For acidic molecules:

\[ \text{HA} \rightleftharpoons H^+ + A^- \]

\[ \text{pK}_a = \text{pH} + \log [\text{HA}]/[\text{A}^-] \]

For basic molecules:

\[ \text{BH}^- \rightleftharpoons B + H^+ \]

\[ \text{pK}_b = \text{pH} + \log[\text{BH}^-]/[\text{B}] \]

Drugs will tend to exist in the ionized form when exposed to an environment with a pH opposite to their own state. Therefore acids become increasingly ionized with increasing pH (i.e. basic). It is useful to consider three important body compartments to plasma (pH = 7.4), stomach (pH = 2) and urine (pH = 8). Examples include the following.

- Aspirin is a weak acid (pKₐ = 3.5) and its absorption will therefore be favoured in the stomach, where it is uncharged, and not in the plasma or the urine, where it is highly charged; aspirin in high doses may even damage the stomach.
- Morphine is a weak base (pKₐ = 8.0) that is highly charged in the stomach, quite charged in the plasma, and half charged in the urine. Morphine can cross the blood–brain barrier but is poorly and erratically absorbed from the stomach and intestines, and metabolized by the liver; it must, therefore be given by injection or delayed-release capsules.
- Some drugs, such as quaternary ammonium compounds (e.g. suxamethonium, tubocurarine), are always charged and must, therefore be injected or inhaled (e.g. tiotropium bromide).

Drug distribution

Once drugs have reached the circulation, they are distributed around the body. Because most drugs have a very small molecular size, they can leave the circulation by capillary filtration to act on the tissues.

The half-life of a drug (t½) is the time taken for the plasma concentration of that drug to fall to half of its original value. Bulk transfer in the blood is very quick.

- Drugs exist either dissolved in the blood or bound to plasma proteins such as albumin. Albumin is the most important circulating protein for binding many acidic drugs.
- Drugs that are basic tend to be bound to a globulin fraction that increases with age. A drug that is bound is confined to the vascular system and is unable to exert its actions; this becomes a problem if more than 80% of the drug is bound.
- Drugs can interact, and one drug may displace another. For example, aspirin can displace the benzodiazepine diazepam from albumin.

The apparent volume of distribution (Vd) is the calculated pharmacokinetic space in which a drug is distributed.

\[ V_d = \frac{\text{dose administered}}{\text{initial apparent plasma concentration}} \]
• $V_d$ values that amount to less than a certain body compartment volume indicate that the drug is contained within that compartment. For example, when the volume of distribution is less than 5 L, it is likely that the drug is restricted to the vasculature.

• $V_d$ values less than 15 L implies that the drug is restricted to the extracellular fluid.

• $V_d$ values greater than 15 L suggests distribution within the total body water. Some drugs (usually basic) have a volume of distribution that exceeds body weight, in which case tissue binding is occurring. These drugs tend to be contained outside the circulation and may accumulate in certain tissues. Very lipid-soluble substances, such as thiopental, can build up in fat. Mepacrine, an antimalarial drug, has a concentration in the liver 200 times that in the plasma because it binds to nucleic acids. Some drugs are even actively transported into certain organs, for example, iodine hormones accumulate in the thyroid.

**CLINICAL NOTE**

Anaesthetists need to consider the weight of their patient before administering thiopental given that it is a highly lipid soluble medication that will accumulate in the fat of obese patients and thus have a longer half-life than in a thinner patient.

**Drug metabolism**

Before being excreted from the body, most drugs are metabolized. A small number of drugs exist in their fully ionized form at physiological pH (7.4) and, owing to this highly polar nature, are metabolized to only a minor extent, if at all. The sequential metabolic reactions that occur have been categorized as phases 1 and 2.
Sites of metabolism
The liver is the major site of drug metabolism although most tissues can metabolize specific drugs. Other sites of metabolism include the kidney, the lung and the gastrointestinal tract. Diseases of these organs may therefore affect a drug’s pharmacokinetics.

Orally administered drugs, which are usually absorbed in the small intestine, reach the liver via the portal circulation. At this stage, or within the small intestine, the drugs may be extensively metabolized; this is known as the first-pass metabolism and means that considerably less drug reaches the systemic circulation than enters the portal vein (see Fig. 1.10). This causes problems because it means that higher doses of the drug must be given and, owing to individual variation in the degree of the first-pass metabolism, the effects of the drug can be unpredictable. Drugs that are subject to a high degree of the first-pass metabolism, such as the local anaesthetic lidocaine, cannot be given orally and must be administered by some other route.

Phase 1 metabolic reactions
Phase 1 metabolic reactions include oxidation, reduction and hydrolysis. These reactions introduce a functional group, such as OH− or NH₂, which increases the polarity of the drug molecule and provides a site for phase 2 reactions.

Oxidation
Oxidations are the most common type of reaction and are catalysed by an enzyme system known as the microsomal mixed function oxidase system, which is located on the smooth endoplasmic reticulum. The enzyme system forms small vesicles known as microsomes when the tissue is homogenized.

- Cytochrome P₄₅₀ is the most important enzyme, although other enzymes are involved. This enzyme is a haemoprotein that requires the presence of oxygen, reduced nicotinamide adenine dinucleotide phosphate (NADPH) and NADPH cytochrome P₄₅₀ reductase to function.
• It exists in several hundred isoforms, some of which are constitutive, whereas others are synthesized in response to specific signals. The substrate specificity of this enzyme depends on the isoform but tends to be low, meaning that a whole variety of drugs can be oxidized.

Although oxidative reactions usually result in inactivation of the drug, sometimes a metabolite is produced that is pharmacologically active and may have a duration of action exceeding that of the original drug. In these cases, the drug is known as a prodrug, for example, codeine that is demethylated to morphine.

**Reduction**

Reduction reactions also involve microsomal enzymes but are much less common than oxidation reactions. An example of a drug subject to reduction is prednisone, which is given as a prodrug and reduced to the active glucocorticoid prednisolone.

**Hydrolysis**

Hydrolysis is not restricted to the liver and occurs in a variety of tissues. Aspirin is spontaneously hydrolysed to salicylic acid in moisture.

**Phase 2 metabolic reactions**

Drug molecules possessing a suitable site that was either present before phase 1 or is the result of a phase 1 reaction, are susceptible to phase 2 reactions. Phase 2 reactions involve conjugation, the attachment of a large chemical group to a functional group of the drug molecule. Conjugation results in the drug being more hydrophilic and thus more easily excreted from the body.

• In conjugation it is mainly the liver that is involved, although conjugation can occur in a wide variety of tissues.
• Chemical groups involved are endogenous activated moieties such as glucuronic acid, sulphate, methyl, acetyl and glutathione.
• The conjugating enzymes exist in many isoforms and show relative substrate and metabolite specificity.

Unlike the products of phase 1 reactions, the conjugate is almost invariably inactive. An important exception is morphine, which is converted to morphine 6-glucuronide, which has an analgesic effect lasting longer than that of its parent molecule.

**Factors affecting metabolism**

Enzyme induction is the increased synthesis or decreased degradation of enzymes and occurs as a result of the presence of an exogenous substance. Examples include the following.

• Some drugs can increase the activity of certain isoenzyme forms of cytochrome P<sub>450</sub> and thus increase their own metabolism, as well as that of other drugs.
• Smokers can show increased metabolism of certain drugs because of the induction of cytochrome P<sub>450</sub> by a constituent in tobacco smoke.
• In contrast, some drugs inhibit microsomal enzyme activity and therefore increase their own activity as well as that of other drugs.

Table 1.3 gives some examples of enzyme-inducing agents, and the drugs whose metabolism is affected. Competition for a metabolic enzyme may occur between two drugs, in which case there is a decreased metabolism of one or both drugs. This is known as inhibition.

Enzymes that metabolize drugs are affected by many aspects of diet, such as the ratio of protein to carbohydrate, flavonoids contained in vegetables, and polycyclic aromatic hydrocarbons found in barbequed foods.

**Overdose**

Drugs that are taken at 2 to 1000 times their therapeutic dose can cause unwanted and toxic effects. Paracetamol can be lethal at high doses (2–3 times the maximum therapeutic dose), owing to the accumulation of its metabolites.

In phase 2 of the metabolic process, paracetamol is conjugated with glucuronic acid and sulphate. When high doses of paracetamol are ingested, these pathways become saturated and the drug is metabolized by the mixed

| Table 1.3 Examples of drugs that induce or inhibit drug-metabolizing enzymes |
|---------------------------------|---------------------------------|
| **Drugs modifying enzyme action** | **Drugs whose metabolism is affected** |
| Phenobarbital and other barbiturates | Warfarin |
| Rifampicin | Oral contraceptives |
| Phenytoin | Corticosteroids |
| Ethanol | Cyclosporine |
| Carbamazepine |
| **Enzyme inhibition** |
| Allopurinol | Azathioprine |
| Chloramphenicol | Phenytoin |
| Corticosteroids | Various drugs—TCA, cyclophosphamide |
| Cimetidine | Many drugs—amiodarone, phenytoin, pethidine |
| MAO inhibitors | Pethidine |
| Erythromycin | Cyclosporine |
| Ciprofloxacin | Theophylline |

function oxidases. This results in the formation of the toxic metabolite $N$-acetyl-$p$-benzoquinone which is inactivated by glutathione. However, when glutathione is depleted, this toxic metabolite reacts with nucleophilic constituents in the cell leading to necrosis in the liver and kidneys.

$N$-Acetylcysteine or methionine can be administered in cases of paracetamol overdose, because these increase liver glutathione formation and the conjugation reactions, respectively.

**Drug excretion**

Drugs are excreted from the body in a variety of different ways. Excretion predominantly occurs via the kidneys into urine or by the gastrointestinal tract into bile and faeces. Volatile drugs are predominantly exhaled by the lungs into the air. To a lesser extent, drugs may leave the body through breast milk and sweat.

The volume of plasma cleared of drug per unit time is known as the clearance.

**Renal excretion**

Glomerular filtration, tubular reabsorption (passive and active), and tubular secretion all determine the extent to which a drug will be excreted by the kidneys.

Glomerular capillaries allow the passage of molecules with a molecular weight less than 20 000. The glomerular filtrate thus contains most of the substances in plasma except proteins.

- In the glomerular capillaries the negative charge of the corpuscular membrane repels negatively charged molecules, including plasma proteins.
- In addition, drugs that bind to plasma proteins such as albumin will not be filtered.

Most of the drug in the blood does not pass into the glomerular filtrate but passes into the peritubular capillaries of the proximal tubule where, depending on its nature, one of two transport mechanisms will transport it into the lumen of the tubule. One transport mechanism deals with acidic molecules, the other with basic molecules.

- In the peritubular capillaries tubular secretion is responsible for most of the drug excretion carried out by the kidneys and, unlike glomerular filtration, allows the clearance of drugs bound to plasma proteins. Competition between drugs that share the same transport mechanism may occur, in which case the excretion of these drugs will be reduced.
- Reabsorption of a drug will depend upon the fraction of molecules in the ionized state, which is in turn dependent on the pH of the urine.
- Renal disease will affect the excretion of certain drugs. The extent to which excretion is impaired can be deduced by measuring 24-hour creatinine clearance.

**Gastrointestinal excretion**

Some drug conjugates are excreted into the bile and subsequently released into the intestines where they are hydrolysed back to the parent compound and reabsorbed. This “enterohepatic circulation” prolongs the effect of the drug.

**Mathematic aspects of pharmacokinetics**

**Kinetic order**

Two types of kinetics, related to the plasma concentration of a drug, describe the rate at which a drug leaves the body.

- Zero-order kinetics (Fig. 1.11A) describes a decrease in drug levels in the body that is independent of the plasma concentration, and the rate is held constant by a limiting factor, such as a cofactor of enzyme availability.
When the plasma concentration is plotted against time, the decrease is a straight line. Alcohol is an example of a drug that displays zero-order kinetics.

- **First-order kinetics** (Fig. 1.11B) is displayed by most drugs. It describes a decrease in drug levels in the body that is dependent on the plasma concentration because the concentration of the substrate (drug) is the rate-limiting factor. When the plasma concentration is plotted against time, the decrease is exponential.

**One-compartment model**

The one-compartment model usually gives an adequate clinical approximation of drug concentration by considering the body to be a single compartment. Within this single compartment, a drug is absorbed, immediately distributed, and subsequently eliminated by metabolism and excretion.

If the volume of the compartment is $V_d$ and the dose administered $D$, then the initial drug concentration, $C_o$, will be:

$$C_o = \frac{D}{V_d}$$

The time taken for the plasma drug concentration to fall to half of its original value is the half-life of that drug. The decline in concentration may be exponential, but this situation expresses itself graphically as a straight line when the log plasma concentration is plotted against the time after intravenous dose (Fig. 1.12A).

Half-life is related to the elimination rate constant ($K_{el}$) by the following equation:

$$t_{1/2} \times K_{el} = \text{natural log} \ 2 \left( \ln 2 \right)$$

Half-life is related to $V_d$, but does not determine the ability of the body to remove the drug from the circulation, because both $V_d$ and half-life change in the same direction. The body’s ability to remove a drug from the blood is termed clearance ($Cl_p$) and is constant for individual drugs.

$$Cl_p = V_d \times K_{el}$$

If the drug is not administered parenterally, plotting the log plasma drug concentration against time will require the consideration of both absorption and elimination from the compartment (Fig. 1.12B).

The one-compartment model is widely used to determine the dose of the drug to be administered. The two-compartment model expands on this model by considering the body as two compartments to allow some consideration of drug distribution.

**Model-independent approach**

For drugs displaying first-order kinetics, the level of the drug in the body increases until it is equal to the level excreted, at which point steady-state is reached (Fig. 1.13), such that:

- The time to reach steady-state is usually equal to four to five half-lives.
- The amount of drug in the body at steady-state will depend upon the frequency of drug administration: the greater the frequency, the greater the amount of drug and the less the variation between peak and trough plasma concentrations. If the frequency of administration is greater than the half-life, then an accumulation of the drug will occur.

The loading dose can be calculated according to the desired plasma concentration at steady-state ($C_{ss}$) and the volume of distribution ($V_d$) of the drug:

$$\text{Loading dose (mg/kg)} = V_d (L/kg) \times C_{ss} (mg/L)$$

**Adherence**

Lastly, despite not being a pharmacological property, it is important to consider adherence. For some drugs to be effective (e.g. antibiotics), they must be taken at regular intervals and for a certain period of time. Adherence can be an issue in paediatric and elderly patients. With children, parents must remember to give the medicine and follow directions.
Drug interactions and adverse effects

accurately; the child must cooperate and not spit out or spill
the medicine. Similarly, elderly patients’ capacity to under-
stand and remember to take their medicines must be ascer-
tained, as well as their physical ability to carry out the task.
For example, an elderly patient with arthritis may struggle to
administer medicines unaided. Furthermore, adherence is
limited if patients are required to take several medications.
Practical dosage forms are important in achieving ad-
herence. Many tablets are now sugar coated, making them
easier to take, and a large number of the drugs manufac-
tured for children are in the form of elixirs or suspensions,
which may be available in a variety of different flavours,
making their administration less of a problem.
The route of administration of a drug may affect adher-
ence. Taking a drug orally, for example, is simpler than in-
jecting it. The wide variety of devices available to deliver
inhaled drugs are often challenging because this may re-
quire good coordination to work properly, something the
young, infirm and elderly find difficult.
The dosing schedule is also an important aspect of ad-
herence. The easier this is to follow, and the less frequently
a drug needs to be taken or administered, the more likely
adherence will be achieved.

**Drug interactions**

Drugs interact in a number of ways that may produce un-
wanted effects. Two types of interactions exist: pharmaco-
dynamic and pharmacokinetic.

**Pharmacodynamic interactions**

Pharmacodynamic interactions involve a direct conflict
between the effects of drugs. This conflict results in the
effect of one of the two drugs being enhanced or reduced.
Examples include the following:

- Propranolol, a β-adrenoceptor antagonist given for
  angina and hypertension, will reduce the effect of
  salbutamol, a β₂-adrenoceptor agonist given for the
  treatment of asthma. The administration of beta-
  blockers to asthmatics should therefore be avoided, or
  undertaken with caution.
- Administration of monoamine oxidase inhibitors, which
  inhibit the metabolism of catecholamines, enhances the
  effects of drugs such as ephedrine. This enhancement
  causes the release of noradrenaline from stores in the
  nerve terminal and is known as potentiation.

**Pharmacokinetic interactions**

Absorption, distribution, metabolism and excretion all
affect the pharmacokinetic properties of drugs. Thus any
drug that interferes with these processes will be altering
the effect of other drugs.

- If administered with diuretics, nonsteroidal
  antiinflammatory drugs (NSAIDs) will reduce the
  antihypertensive action of these drugs. NSAIDs bring
  about this effect by reducing prostaglandin synthesis
  in the kidney, thus impairing renal blood flow and
  consequently decreasing the excretion of waste and
  sodium. This results in an increased blood volume and
  a rise in blood pressure.
- Enzyme induction, which occurs as a result of the
  administration of certain drugs, can affect the metabolism
  of other drugs served by that enzyme (see Table 1.3).
  In some cases, however, drugs are used together so that
  their interaction can bring about the desired effect.
- For example, carbidopa is a drug used in conjunction
  with levodopa (l-dopa) in the treatment of Parkinson
  disease. l-Dopa, which is converted to dopamine in
  the body, can cross the blood–brain barrier. Carbidopa
  prevents the conversion of l-dopa to dopamine;
  however, it cannot cross the blood–brain barrier and
  so acts to reduce the peripheral side effects while still
  allowing the desired effects of the drug.

**Fig. 1.13** Log plasma drug concentration versus time plot
for a drug administered by mouth every 6 hours when its
terminal disposition half-life is 6 hours.

**Clinical Note**

Mr Abbas is a 66-year-old man who takes metoprolol,
a β-blocker, for his hypertension. He had a myocardial
infarction 2 days ago and has now developed
ventricular tachycardia (a type of cardiac arrhythmia).
He was given amiodarone (a class III antiarrhythmic
agent) to slow down his heart rate. Because
amiodarone inhibits the cytochrome P₄₅₀ enzymes
responsible for breaking down metoprolol, there is
a risk that the plasma concentration of metoprolol
would be higher than expected. The prescribing
doctor, therefore needs to monitor for an excessive
slow beating of the heart and for heart block.
Adverse effects

As well as interacting with one another and with their target tissue, drugs will also interact with other tissues and organs and alter their function. No drug is without side effects, although the severity and frequency of these will vary from drug to drug and from person to person.

The liver and the kidneys are susceptible to the adverse effects of drugs, as these are the sites of drug metabolism and excretion. Some drugs cause hepatotoxicity or nephrotoxicity.

Some people are more prone to the adverse effects of drugs.

- Pregnant women must be careful about taking certain medications that are teratogenic, that is, cause foetal malformations (e.g. thalidomide taken in the 1960s for morning sickness).
- Breastfeeding women must also be careful about which drugs they take, because many drugs can be passed on in the breast milk to the developing infant.
- Patients with an underlying illness, such as liver or kidney disease. These illnesses will result in decreased metabolism and excretion of the drug and will produce the side effects of an increased dose of the same drug.
- Elderly people who tend to take a large number of drugs have an increased risk of drug interactions and the associated side effects. In addition, elderly patients have a reduced renal clearance and a nervous system that is more sensitive to drugs. The dose of drug initially given is usually 50% of the adult dose, and certain drugs are contraindicated.
- Children, like the elderly, are at an increased risk of toxicity because of immature clearance systems.
- Patients with genetic enzyme defects, such as glucose 6-phosphate dehydrogenase deficiency. The deficiency will result in haemolysis if an oxidant drug, such as aspirin, is taken.

Certain drugs are carcinogenic, that is, induce cancer. Allergic reactions to certain drugs are common, occurring in 2% to 25% of cases. Most of these are not serious, for example, skin reactions; however, rarely, reactions such as anaphylactic shock (type 1 hypersensitivity) occur that may be lethal, unless treated with intramuscular adrenaline. The most common allergic reaction is to penicillin, which produces an anaphylactic shock in approximately 1 in 50,000 people.

HINTS AND TIPS

Adverse reactions and allergy to a drug are different. Adverse reactions are usually minor irritations, whereas an allergic reaction can be life threatening.
Drug development

Hundreds of thousands of substances have been produced by the pharmaceutical industry over the past 50 years, although very few ever get past preclinical screening, and fewer than 10% of these survive clinical assessment.

There are four stages a potential drug goes through from discovery to being approved (Table 1.4).

Phase 4 can be regarded as an ongoing phase, where drugs are monitored once licensed for general use. By this stage, the efficacy and dose–response relationship are known, although the side-effect profile is often incomplete, and information is gathered on these “adverse reactions” which are caused by, or likely caused by new drugs.

In the United Kingdom, this is known as the yellow card scheme. The British National Formulary (BNF) contains detachable yellow cards, which medical staff complete, documenting adverse drug reactions in their patients, which can then be forwarded to the Medicines Control Agency. The Medicines Control Agency collates these data and uses them for surveillance of common or severe adverse effects. The data are publicized in future copies of the BNF, or used in the reassessment of certain drug licences.

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HINTS AND TIPS

The salient points of the drug history are:
• current and previous drugs and their doses
• adverse drug reactions and allergies
• family history of allergies
• recreational drug use
• existing renal or hepatic and general disease.

Chapter Summary

• Drugs can produce their effects by targeting specific cellular macromolecules, often proteins. The majority act via receptors in cell membranes but they can also work on transporter molecules and enzymes.
• Interaction with ligand-gated ion channels (ionic receptors) results in hyperpolarization or depolarization. Interaction with G protein-coupled receptors (metabotropic) results in secondary messenger involvement and either calcium release or protein phosphorylation. Kinase-linked receptor activation results in protein phosphorylation which induces gene transcription and protein synthesis. Nuclear receptor activation results in gene transcription and protein synthesis.
• Drugs can be administered topically, enterally, or parenterally. Drug excretion, metabolism and dosage can be modelled by pharmacokinetics to relate to plasma concentration of a drug.
• Drugs can interact in unwanted ways, involving pharmacokinetics and pharmacodynamics. Adverse drug effects stem from the drug interacting with tissues and organs to alter their function. Adverse reactions are usually minor, whereas allergic reactions can be life-threatening.
• Drug development is divided into preclinical and then 4 subsequent phases involving ever larger trials. Phase 4 is postmarketing surveillance and is always ongoing once the drug is in the market.