CHAPTER 18

PRINCIPLES OF DRUG ACTION

Every substance, medicine or poison that a person takes alters the biochemistry of cells and has a physiological effect on the body's systems. The aim of this chapter is to enable healthcare professionals to become familiar with some of the key concepts related to the action of the main classes of agents, using a few commonly prescribed drugs to illustrate some important aspects of pharmacology.

18.1 Pharmacology

Pharmacology is the science of the composition, actions and uses of drugs and other agents and their effects on the human body (→ Box 18.1). The subject links physiology with both chemistry and pathology. Pharmacology has a long history that originates with the use of naturally occurring substances, many derived from plant material, for the treatment of ailments, e.g. digitalis was purified from foxgloves and aspirin was derived from willow bark. During the 20th century, rapid developments in knowledge of drug action on the body led to many new compounds being synthesised in laboratories by the pharmaceutical industry (→ Box 18.2).

Several key concepts are central for understanding the action of drugs on the human body:

- **pharmacokinetics** – the study of the way the body processes a drug, which includes ingestion, metabolism and elimination
- **pharmacodynamics** – the study of the physiological, biochemical and molecular effects of drugs and any side-effects they cause
- **pharmacogenomics** – the study of how genes affect an individual's response to drugs.

18.2 Pharmacokinetics

Drugs enter the body by a **route of administration**, and most drugs can be administered via several of the routes below, although at different dosages (→ Box 18.3).

18.2.1 Oral route

The oral route (**PO**; ***per os***) is by mouth into the digestive system and many drugs are administered in this way. After ingestion, drugs reach the small intestine which has a large blood supply, so absorption of some substances can be quite rapid.

- Food may affect the rate of absorption of some drugs. Therefore, some prescribed medications are taken on an empty stomach.
- Drugs taken orally should be followed by a drink of water to help with swallowing.
- The oral route is unsuitable for people who have difficulties in swallowing pills or are 'nil by mouth' before surgical procedures.
- Drugs that are broken down by enzymes in the stomach, e.g. insulin, are not usually administered by an oral route because absorption can be unpredictable (→ Box 18.4).

Box 18.1 A **pharmacological agent** is a biologically active substance applied to the body for its therapeutic effects on one or more tissues or organs. Many agents are therapeutic drugs but the term also includes anticancer agents and antidiabetic agents.

Box 18.2 Pharmacists are trained in the use of thousands of different **agents** that affect living systems, e.g. drugs used as medications, substances that may be abused, and other chemicals that interact with the human body including hormones, food additives, poisons and insecticides.

Box 18.3 When a drug is prescribed, the patient should be informed of:

- how and when to take the drug
- how soon it takes effect
- how long it is active for
- possible adverse effects
- advice on missed doses, storage and overdosing.

Box 18.4 Nausea can be the body's natural response to ingesting a noxious substance, with the **vomiting reflex** ensuring that the substance is emptied from the stomach. But not all nausea is desirable and **anti-emetic drugs** can be effective for the management of a wide range of causes of vomiting and nausea.

18.2.2 Injection route

Injected drugs are forced into subcutaneous tissues, a vein (intravenous; IV) or a muscle (intramuscular; IM). This method produces a more rapid response than oral or rectal routes and also bypasses the sometimes unpredictable absorption process of the gastrointestinal (GI) tract. It is also useful for unconscious or uncooperative patients. Injection requires sterile conditions and once injected, the drug cannot be retrieved. There may be pain at the injection site, and it is more costly than other routes of administration.

Intravenous route (IV). The drug is injected into a vein and provides a rapid response as it is almost instantaneously delivered by circulation to its site of action. This is an effective route for drugs which would be poorly absorbed or ineffective if delivered orally, and the dose can be titrated against the person's response to the drug.

Intramuscular (IM) and **subcutaneous routes** allow a 'depot' of drug to be administered which can be released slowly into the circulation over a period of days or weeks, e.g. antipsychotic agents which can be active for several months.

Intravitreal route is injection into the eyeball.

Intrathecal route is epidural injection into meningeal spaces of the spine.

18.2.3 Sublingual route

The drug is usually placed directly under the tongue (**sublingual**; SL) where a dense capillary network enables it to be absorbed rapidly into the bloodstream.

- A range of pharmaceutical preparations dissolve easily in saliva and are delivered sublingually, e.g. lozenges, sprays, vaccines and strips.
- Often the taste of a drug limits the possibility of delivery by this route, e.g. bitter compounds are unpalatable (→ Box 18.5).

Box 18.5 Before medication is administered, the patient's 'six rights of medication' are checked. These are:

- the right individual
- the right medication
- the right dose
- the right time
- the right route
- the right documentation.

18.2.4 Topical route

The topical (also known as transdermal; TD) route includes salves, lotions, creams, ointments and patches.

- Medicated patches are sometimes used to deliver controlled doses of a drug in a single delivery which avoids difficulties such as nausea or diarrhoea, e.g. opioid patches for pain relief or oestrogen patches for the management of peri-menopausal symptoms.
- Passage through damaged skin is faster than through intact skin, e.g. about 80% of a dose of hydrocortisone can pass through damaged, inflamed skin compared with only 1% of the same dose through intact skin.
- Many transdermal preparations contain chemical permeation enhancers (CPEs) to facilitate absorption of the drug.
- The transdermal route is non-invasive, with a relatively high level of patient satisfaction.

18.2.5 Rectal route

Medications administered by the rectal route (per rectum; **PR**) usually come in the form of suppositories which melt at body temperature or as enemas which are liquid preparations. The rectum is the final 20 cm of the gastrointestinal tract and has a highly vascular lining.

- This route allows fast absorption and high bioavailability of drugs.
- Drugs administered through the rectum cause less nausea and are less likely to be altered before they reach the systemic circulation. The route is also useful if people have dysphagia (difficulty in swallowing) or bowel obstruction.
- Patients must be informed about, and consent to, receiving drugs per rectum.
- Cultural diversity and individual sensitivities always need to be considered.

18.2.6 Inhalation route

An inhaled drug is delivered into the person's airway via an aerosol, spray, mist or nebuliser. The respiratory epithelium has a vast surface area of capillaries so delivery of bronchodilators and other respiratory agents can be rapid and targeted to the lungs. Sometimes a metered dose is delivered via a nebuliser and on other occasions it is self-administered from a canister, e.g. salbutamol for the management of asthma.

- Absorption depends on the size of drug particle and the patient's technique, e.g. with inhalers and nebulisers.
- Supplemental oxygen is usually delivered via nasal prongs and inhaled.
- Drugs that get deposited in the airway (trachea) are removed by mucociliary clearance.

18.3 Drug absorption

Drugs administered by the oral, sublingual, transdermal and inhalation routes have to be absorbed into the bloodstream. To achieve this, each drug must cross semipermeable membranes before it can enter the circulation. How a drug is absorbed depends on the physical and chemical characteristics of the substance.

- Lipid-soluble drugs can pass through the mucous membranes of the mouth.
- The stomach favours absorption of weakly acid drugs, e.g. aspirin.
- The small intestine favours weakly basic (alkaline) drugs, e.g. morphine.
- The presence of food in the GI tract may affect the rate of absorption.
- The inactive ingredients, such as 'binders' in a tablet or capsules, affect how rapidly the drug will dissolve and be absorbed.
- Drugs administered by the oral routes are carried by the **hepatic portal system** from the intestines to the liver, where the absorbed drug is subject to first pass metabolism (→ 18.6). This process allows some drugs to be chemically altered in the **liver** before reaching the systemic circulation.
- Drugs administered by the sublingual and rectal routes enter the venous circulation and hence bypass **first pass metabolism** in the liver before reaching the systemic circulation.

18.3.1 Bioavailability

Bioavailability is determined by the physical and chemical properties of the substance, rate of gastric emptying and any interactions with other drugs. The term describes the portion of a drug that reaches the systemic circulation unchanged.

When administered intravenously, the bioavailability of a drug is 100%; when taken orally, the amount reaching the bloodstream depends on whether absorption is complete or incomplete, on the extent of first pass metabolism (→ 18.6) and differences between patients.

18.3.2 Bound and free molecules

Drug molecules circulating in the bloodstream exist in two forms: 'bound' and 'free':

- '**bound**' means that the drug molecules are attached to circulating plasma protein molecules, which inactivates the drug. Many drugs bind reversibly and then are gradually freed, thus the blood is acting as a reservoir for the drug.
- '**free**' means the molecules are not bound to plasma proteins and can therefore diffuse through capillary walls, cross cell membranes and become chemically active or be eliminated.

18.4 Drug distribution

Drug distribution is the transportation of absorbed drugs by the circulatory system and through the interstitial and intracellular compartments of cells (→ Box 18.6). During distribution, a drug is carried to **target sites** where it has an effect, and non-target sites where it may cause side-effects or adverse reactions.

Box 18.6 Distribution of a drug to a tissue depends on a range of factors such as the surface area of the tissue and capillaries, and the chemical composition of the substance and its volume.

Most drugs do not distribute (spread) evenly throughout the body, which means that different tissues can receive different doses of the drug.

- Organs that are highly vascular, such as the brain, kidneys, heart and liver, will acquire a drug more rapidly than those with a reduced blood supply, such as bone and adipose tissue. The patient's level of activity and local tissue temperature may affect drug distribution to skin and muscle.
- Water-soluble drugs tend to stay within the blood, tissue fluid and lymph, and only leave very slowly, because they bind tightly to plasma proteins circulating in the blood.
- Fat-soluble drugs leave the bloodstream more quickly because they bind less tightly to plasma proteins than water-soluble drugs.
- Some drugs accumulate in certain tissues because the tissues there have a special affinity for that drug, e.g. the thyroid gland's affinity for iodine, the heart and skeletal muscles for digoxin, or fatty tissue for fat-soluble drugs.

18.4.1 The blood–brain barrier

The capillary walls in the central nervous system differ from those in other parts of the body. The capillary endothelial cells (→ 9.2.2) fit together more tightly, forming a barrier – a **blood–brain barrier** (BBB) – that separates the circulating blood from the extracellular fluid in the CNS. Substances in solution and fat-soluble compounds can pass through the barrier but large molecules like proteins and particles such as bacteria are excluded. The properties of the blood–brain barrier protect the CNS from many substances harmful to it but can make it difficult for many potentially useful drugs to reach the brain cells.

18.4.2 Placental circulation

The chorionic villi enclose the foetal capillaries. These are separated from the maternal capillaries by a layer of trophoblastic cells (→ Fig. 12.13). This barrier will permit the passage of lipid-soluble, non-ionised compounds from mother to foetus but prevents entrance of those substances that are poorly lipid-soluble. Inefficient elimination of drugs from the growing embryo and foetus's body is experienced by their:

- increased sensitivity to the effects of drugs
- undeveloped abilities to metabolise and excrete drugs.

18.5 Drug metabolism

Drug metabolism is the metabolic (biochemical) breakdown that converts medication into active biochemical substances (→ Box 18.7). Thousands of different chemical substances and agents are prescribed as medication and most are broken down by enzymes in the **liver**. Many different enzymes are responsible for the breakdown and biotransformation of many compounds including pollutants, carcinogens and pesticides as well as drugs – a process which takes place in **three phases**.

Box 18.7 The **half-life** of a drug is defined as the time it takes for its effectiveness to be reduced by half.

Phase I – chemical modification

Chemical modification is the conversion of hydrophobic (water-hating) drugs into hydrophilic ones that are more water-soluble. Enzymes that belong to the **cytochrome P450 (CYP) oxidase** family are membrane-bound within the endoplasmic reticulum of hepatocytes (liver cells) and they catalyse this process. Most of the modified compounds need to undergo phase II and phase III before they can be excreted (→ Box 18.8).

Box 18.8 Phase I reactions take place more slowly in babies and in the elderly.

Phase II – conjugation

Conjugation involves the chemical coupling of the modified compound to polar compounds that are less active, such as glutathione, glucuronic acid, sulphate or glycine. These conjugated compounds are large molecules that cross cell membranes with difficulty. Conjugated molecules are formed by enzymes called **transferases** (→ Box 18.9).

Box 18.9 Some people known as **slow acetylators** have a prolonged phase II process for certain drugs.

Phase III – detoxification

This step involves transporter molecules which secrete unwanted metabolites (products of metabolism) into the lumen of the intestines and into bile and urine for excretion.

18.5.1 Drug elimination

Ideally, in drug therapy, the plasma concentration of the drug reaches a steady state within the therapeutic range so that the rate at which the drug enters the circulation (the dosage rate) equals the rate at which the drug is being eliminated. However, the therapeutic range of a drug will fall as time goes on (→ Box 18.10).

Enzymes located in the endoplasmic reticulum of **hepatocytes** (liver cells) convert drug molecules to water-soluble metabolites which can be easily excreted by the **kidney**, which is the main excretion route. Small amounts are excreted via a number of routes, e.g. in bile, saliva, sweat, tears, perspiration and breast milk. The lungs are a route by which inhaled general anaesthetics can be excreted.

Box 18.10 Clearance of a drug is the volume of blood (or plasma) from which a drug is removed per unit of time, which provides an indication of how effectively the liver and kidneys are eliminating the substance.

18.5.2 Drug metabolism in children

Children cannot simply be perceived as small adults and should be given drugs and medications cautiously. They metabolise drugs differently from adults, may have immature livers, and the longer the half-life of a drug, the higher the risk of adverse reactions.

- Children may have trouble swallowing tablets or liquid medicines.
- Oral drugs may stay in the stomach of children for longer because gastric emptying takes place more slowly.
- Gastrointestinal transit times are longer in children, meaning that drugs remain in contact with intestinal linings for longer.
- Differences in fluid volumes and distribution compared with adults mean that there is relatively more body water through which substances can be distributed.
- Immature kidneys may result in delays in eliminating drug molecules from a child's body.

18.6 First pass metabolism of drugs

Box 18.11 The **systemic circulation** carries the drug in the bloodstream to all the tissues in the body. The target cells that it affects are those with receptors to which molecules of the drug can bind.

First pass metabolism (**first pass effect**) applies to drugs taken orally and is the amount of a drug that is lost on its journey from mouth to the systemic circulation (→ Box 18.11). Drugs administered orally must first pass through the digestive tract and the liver, where they are liable to be metabolised by enzymes, particularly the liver enzymes, and this process can greatly reduce their bioavailability (→ Fig. 18.1). **Bioavailability** is the proportion of a drug that reaches the cells (→ 18.3.1).

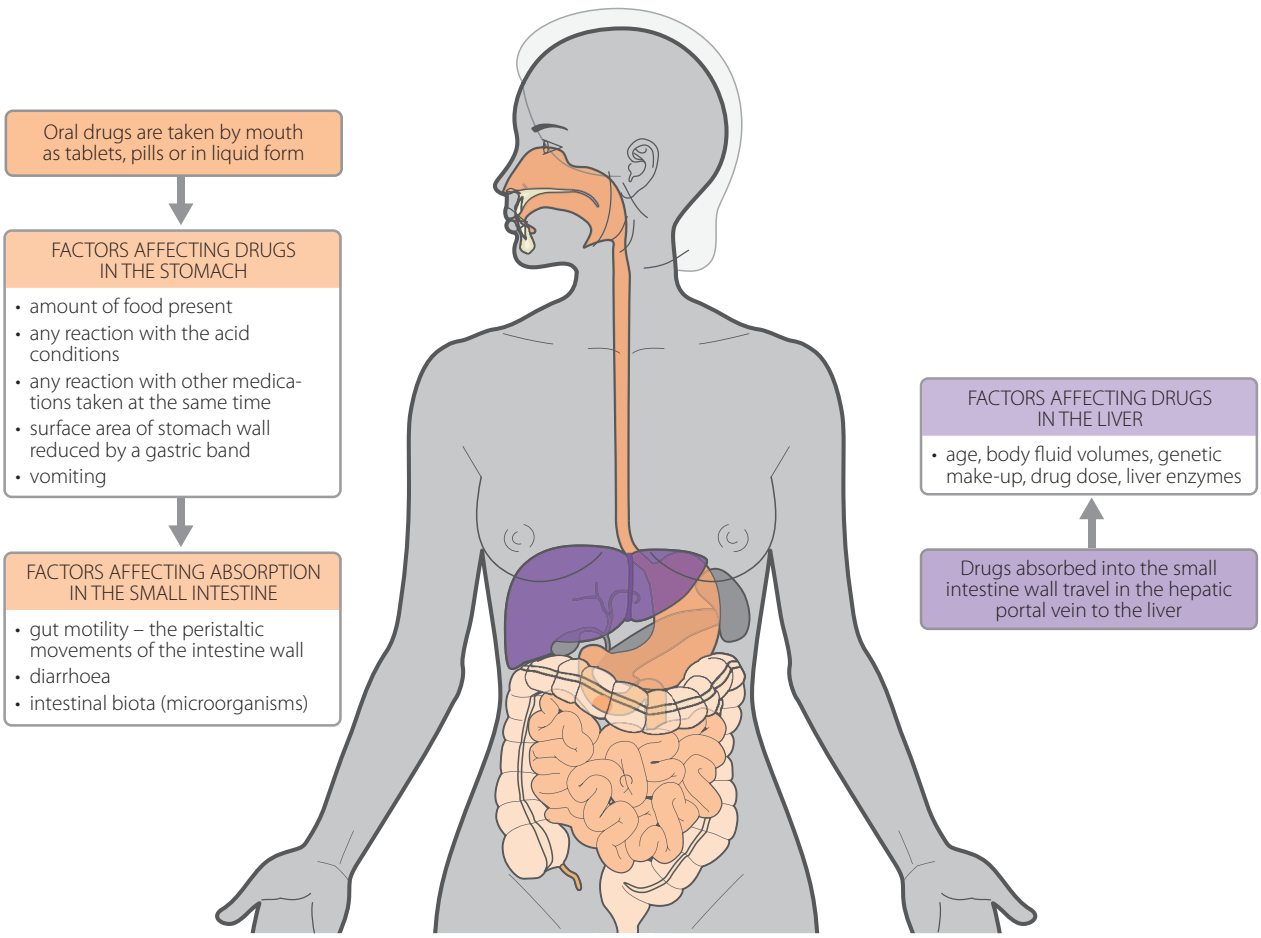

Fig. 18.1 All drugs given by the oral route undergo some metabolism by the gut and the liver which affects their bioavailability.

18.6.1 Avoiding first pass metabolism

Some drugs cannot be administered by the oral route, so adjustments are made to the route and dosage.

- **Injected drugs** cannot be used for oral administration because they are broken down in the digestive tract.
- **Sublingual tablets** dissolve rapidly under the tongue and are absorbed into the mucous membrane then into the rich capillary network underneath.
- **Inhalation** gaseous drugs are delivered across the mucous membranes of the respiratory tract. They are used for asthma and anaesthetics, and produce a rapid response.
- **Suppositories** dissolve in the rectum, vagina or urethra and are absorbed into the bloodstream. This is a useful procedure when patients are vomiting or unable to take medications by mouth.
- **Transdermal patches** deliver a specific dose of medication through the skin and into the bloodstream, e.g. nicotine patches for smoking cessation.

18.6.2 Biotransformation

Biotransformation refers to the way the intensity of a drug effect is determined by metabolic processes in the body:

- Some compounds remain unchanged.
- Some drugs are known as pro drugs because they are inactive until acted upon by the liver, e.g. metabolisation of codeine to morphine.
- Sometimes metabolites (products of metabolic action) are more readily excreted than the parent drug because ionised compounds are more likely to be secreted into urine in the distal tubule (→ 8.2).
- If drugs are rapidly metabolised they may need to be administered more often (2–4 times per day) compared to drugs that are metabolised slowly (once per day).

18.7 Pharmacodynamics

Pharmacodynamics is the branch of science responsible for the understanding of thousands of different chemical agents (chemical substances) that affect living systems. This chapter focuses on physiological actions of a range of agents – therapeutic drugs, hormones, medications, poisons and insecticides – and their interactions with human body systems (→ Box 18.12).

Adverse effects of agents force doctors and health professionals to exercise caution and pay attention to side-effects when prescribing and dispensing any class of agents. Healthcare professionals who administer therapeutic drugs to clients therefore have to be able to:

- understand the mechanism of absorption so that they can explain to the patient why a drug should be taken at a certain time
- communicate information about drugs and their effects to the public and other health and social care workers (→ Box 18.13)
- identify whether the drug has worked as expected
- work out what side-effects a drug may produce
- be aware of symptoms which people may display if they have side-effects or begin to display signs of adverse effects such as toxicity (→ 18.15) when taking a drug.

Box 18.12 There have been many attempts to classify the wide range of drugs that act on the human body and may be used therapeutically. But problems arise because many drugs have complex modes of action and interaction, which makes many classification systems imprecise.

Box 18.13 Therapeutic drugs are natural or artificial substances that are given to treat or prevent illness. Increased understanding of pharmacology and physiology during the 20th century means that the mechanisms of action for many commonly prescribed drugs are completely understood.

18.7.1 Drug actions

The biological effect observed after a drug has been administered is the result of physiological interactions between the drug and the body's cells. It is important for healthcare professionals to be able to distinguish between the action of a drug and its effect:

- **Action of a drug** – the mechanism whereby the chemical substance produces a response in the body. Some drugs act by stimulating a physiological activity or increasing the rate at which it takes place; others inhibit or depress normal physiological functions.
- **Primary effect of a drug** – the desired action of that drug, typically, its therapeutic effect, e.g. chemotherapeutic drugs act to stop cell division in tumour cells and antibiotic agents kill bacteria or stop them from multiplying.
- **Secondary effects of a drug** – any other effects (**side-effects**), which can be harmful or beneficial. Side-effects arise because many drugs are non-specific in nature and alter other normal physiological function(s) as well as the reason for their administration.

Drugs bind to proteins in the body

Most drugs act by binding to a protein. Although there are potentially thousands of different proteins in the human body, drugs mainly act on:

- receptor proteins (→ 18.8.2)
- ion channels (→ 18.9)
- enzymes (→ 18.9.4)
- plasma proteins (→ 5.2.1)
- synapses and neuromuscular junctions (→ 18.11)
- gene expression (→ 18.13).

18.8 Drugs that act on receptor proteins

Receptor proteins are macromolecules which are usually located on plasma membranes of cells (→ Fig. 18.3). Plasma membranes are selectively permeable and the receptor proteins help to regulate cell behaviour. In this chapter '**receptor**' refers to these protein receptors.

Each receptor has its own specific 3-dimensional shape that enables it to bind with a **ligand** (→ Box 18.14). Receptors and their ligands are precisely matched so that:

- most receptors only bind with one specific type of ligand
- ligands may bind with several different receptors.

Box 18.14 A **ligand** is a molecule that binds to a receptor protein. An endogenous ligand is naturally produced within the body's cells; an exogenous ligand comes from outside the body, such as a drug.

18.8.1 Agonist and antagonist ligands

Drug molecules that mimic endogenous ligands and fit closely into receptors either initiate a response (agonists) or change the effect (antagonists) (→ Fig. 18.2).

An **agonist** is a drug that triggers a response in the target cell – a process called **positive efficacy**.

An **inverse agonist** is a drug that binds to the receptor in the same way as an agonist does, but it induces a pharmacological effect opposite to the effect of the agonist.

An **antagonist** is a drug that binds to a receptor and either blocks the response or reduces it. Antagonistic drugs are a large group that work in different ways. They can:

- **inhibit** (stop) an endogenous ligand from binding with the receptor and triggering the response – called **zero efficacy drugs**
- **bind reversibly** with receptors – called **competitive antagonist drugs**
- **bind irreversibly** with receptors – called **irreversible antagonist drugs**.

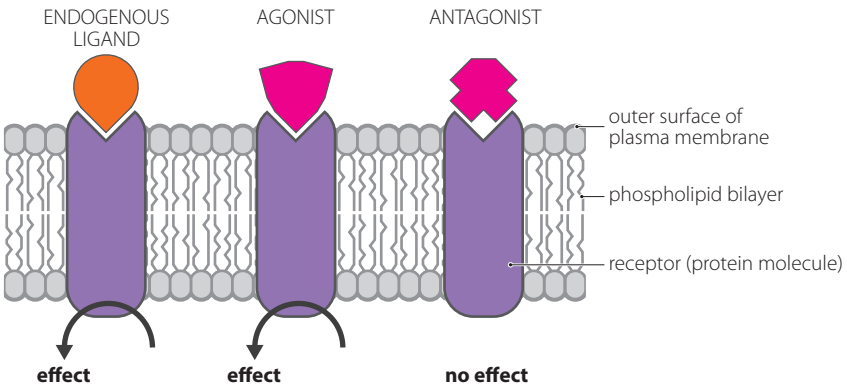

Fig. 18.2 Part of the plasma membrane with ligands binding to receptor proteins.

18.8.2 Drugs that act at ion channels

Essential physiological functions, particularly in excitable tissue (nerve and muscle) depend on movement of electrolytes through highly **selective ion channels** (pores) that are integral proteins within the plasma membrane and intracellular membranes of organelles with openings through which ions can diffuse (→ 20.7.3). The channels allow ions to cross the membrane without coming into direct contact with the hydrophobic core of the phospholipid bilayer. Since channels are important in determining permeability and movement of electrolytes, they are key for the processes of muscle contraction and relaxation, hormone secretion and sensation, as well as homeostatic regulation of electrolyte balance and blood pressure.

Classification of ion channels

Ion channels are usually classified according to whether they are **voltage-gated** (sensitive to changes in membrane potential) or **ligand** (often neurotransmitter)-**gated**, as well as by their molecular shape – active, resting or inactive – and functions. Examples of ion channels include:

- **potassium (K^+) channels** regulate excitability of cells in all parts of the body, influencing cognition, muscle contraction and hormone secretions
- **sodium (Na^+) channels** in excitable cells such as neurons, myocytes and certain types of glia where they are responsible for the rising phase of action potentials (depolarisation)
- **calcium influx** (entry) into many smooth muscle tissues results in depolarisation of the cells.

Examples of drugs and agents that target ion channels

Sodium channels are the molecular targets for drugs used in prevention of acute pain and in treatment of cardiac arrhythmias, epilepsy and bipolar disorder:

- **Local anaesthetic agents** are defined as drugs which reversibly stop transmission of nerve impulses in the region where they are applied without having any effect on consciousness. Many of the drugs achieve the blockade by binding to sodium (Na^+) channels in neuron membranes. Bupivacaine is an example of a local anaesthetic agent and it is used in epidural blocks and in management of postoperative pain.
- **Anticonvulsant drugs** bind to inactivated sodium (Na^+) channels in neurons which helps to stabilise them and reduce seizures in people with epilepsy, e.g. carbamazepine, valproate and phenytoin.

Potassium channel blockers can be used as anti-arrhythmic drugs because K^+ channels play an essential role in repolarising cardiac myocytes. When open, these channels normally allow potassium ions to leave the cells and the electrophysiological changes they induce tend to make the cells less excitable, thus they can reduce tachycardia.

Since there are several different types of K^+ channels in heart cells, the range of available drugs have different actions and are used for different conditions.

Calcium (Ca^{2+}) channel blocking agents stop calcium ions from entering vascular smooth muscle cells. These antagonists induce relaxation of arterioles and reduce peripheral resistance, hence they lower blood pressure, e.g. verapamil and nifedipine.

Benzodiazepines are a family of drugs that act by modulating activity of the GABA (neurotransmitter) receptor, which is a chloride (Cl^-)-selective ion channel. Since activation of the channel reduces excitability of neurons, particularly in the cerebral cortex and limbic systems, so the benzodiazepines tend to have a calming effect. The electrophysiological changes they induce tend to make the cells less excitable, thus they can reduce tachycardia. Other examples of drug classes that affect GABA receptors include barbiturates and general anaesthetics.

Box 18.15 GPCRs form the largest class of proteins that are used as targets for drugs in the human body, accounting for about 50% of all drug sales and prescriptions.

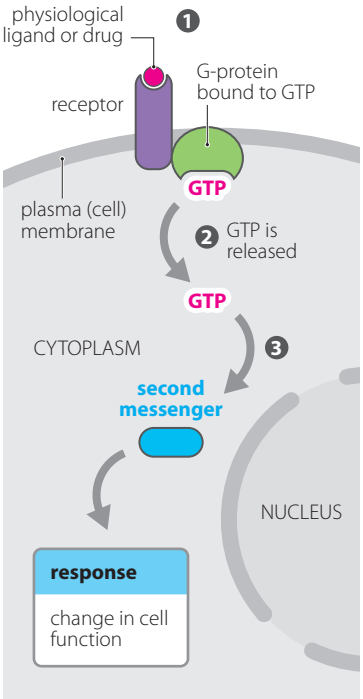

Fig. 18.3 Ligand (natural or drug) binds to G-protein and activates a change in cell function.

18.8.3 Drugs that bind to G-protein coupled receptors

G-protein coupled receptors (GPCRs) are a family of protein receptors that bind with guanosine triphosphate (GTP) (→ Box 18.15). They are responsible for the process of **signal transduction** for many hormones and cell signal molecules which alter the physiological state (→ Fig. 11.2).
When a GTP receptor recognises the ligand, the bound GTP is released and acts rather like a molecular "switch" because it activates (or inhibits) a biochemical system that produces a second messenger chemical inside the cytoplasm. In turn, the second messenger is coupled (linked) to a physiological process inside the cell (→ Fig. 18.3).

Examples of second messengers include cyclic AMP (cAMP), Ca^{2+} ions or inositol-1,4,5-triphosphate ($insP_3$) as shown in Fig. 18.3.

Examples of drugs that bind to G protein receptors

- **Alpha(α)-agonists** (alpha-adrenergic agonists) which selectively stimulate the receptors that would normally respond to the neurotransmitter noradrenaline from the sympathetic nervous system.

Among other effects, these drugs (e.g. phenylephrine and clonidine) induce vasoconstriction of blood vessels.

- **Beta(β)-agonists** are selective agonists of the beta-sub-group of **adrenoreceptors**. Salbutamol exerts its predominant therapeutic effect by acting on beta(β) 2-receptors in bronchial smooth muscles, relaxing them and reducing airway resistance during asthma attacks or exacerbation of COPD (→ 6.7.3).
- **Beta(β)-antagonists** (beta-adrenergic blocking agents) such as bisoprolol and propranolol inhibit the action of the adrenal hormone adrenaline, on heart and blood vessels. Hence these drugs lower blood pressure and can protect against heart attacks and heart failure.
- Many **antihistamine agents** are inverse agonists of histamine receptors, e.g. loratadine is used for the relief of allergy symptoms.

18.8.4 Drugs that bind to nuclear receptors

Nuclear receptors are different from other classes of receptor because of their ability to control the expression of genomic DNA. Many of the ligands for nuclear receptors are lipophilic and are able to cross the plasma membrane and enter the cytoplasm before binding. The activated receptor complex then enters the nucleus and binds to target elements of **DNA molecules** (→ Fig. 18.4). There are a large number of intermediate steps between activation of the receptor and changes in protein synthesis, so the cellular and physiological effects of nuclear receptor activation on gene expression normally take hours.

Nuclear receptors are sometimes called **transcription factors**; they can induce synthesis of specific mRNA or repress genes by inhibiting transcription. They can also have relatively rapid, non-genomic effects through second messenger systems (→ 18.9.1).

Examples of drugs that act at nuclear receptors

This class of receptor includes thyroid hormone receptor (THR), vitamin D receptor (VDR) and receptors for steroid hormones (oestrogen, testosterone, cortisol and progesterone).

- **Thyroxine replacement therapy** is used if people develop hypothyroidism.
- **Steroid hormones** such as hydrocortisone, cortisone or prednisolone are used for anti-inflammatory therapy because they suppress all phases of the inflammatory response. Steroids can sometimes produce striking responses, but high and/or prolonged doses can cause severe side-effects.
- **Contraceptive steroids** – combinations of oestrogens and progestins – are a major method of birth control in many countries.
- **Selective oestrogen receptor modulators** (SERMs), like tamoxifen, behave as oestrogen receptor antagonists in breast tissue. SERMs are used to treat breast cancer in people who have tumours that contain oestrogen receptors; the cancerous cells are inhibited from growing.

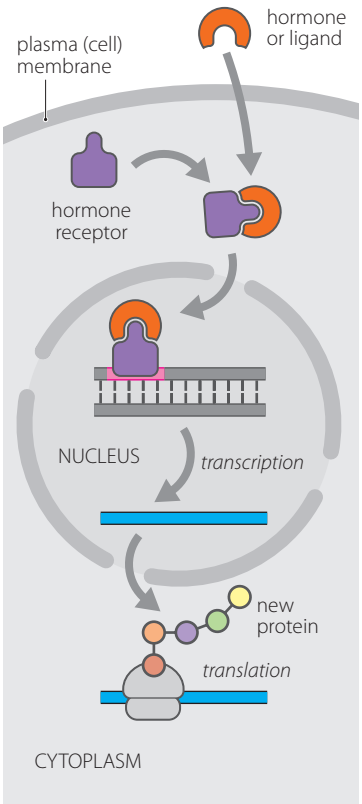

Fig. 18.4 Activation of a nuclear receptor results in gene expression and protein synthesis.

18.8.5 Drugs that act at enzyme-linked receptors

This is a large and diverse group of receptors which span cell membranes and have enzymatic activity (→ Box 18.16). When the endogenous ligand binds to the extracellular (surface) part of the receptor, catalytic (enzyme) activity on the cytoplasmic side of the receptor is triggered. The resultant cascade of enzyme activity requires energy from ATP and ultimately leads to

Box 18.16 The family of enzyme-linked receptors plays a regulatory role in the survival of cells and hence is the target for many innovative anticancer agents including monoclonal antibodies.

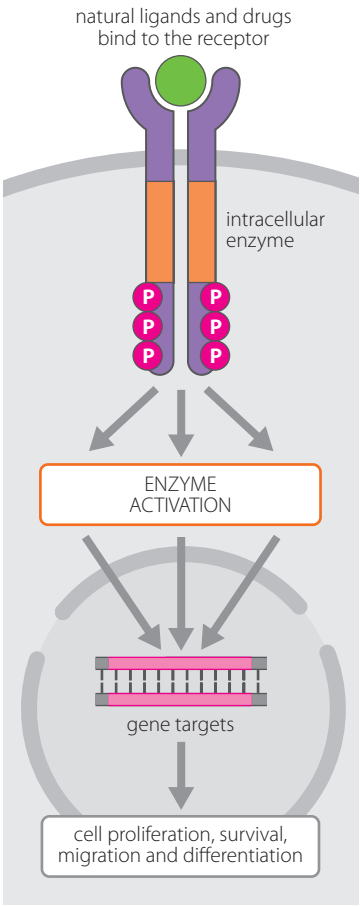

Fig. 18.5 Drugs can act as ligands for enzyme-linked receptors.

Box 18.17 Enzymes are macromolecules (usually proteins) that act as biological catalysts, which means that they speed up biochemical reactions that take place in cells without being used up or being changed themselves. The 3D shape of the enzyme molecule is vital for its ability to bind in a lock-and-key manner to drug molecules. Each enzyme acts on a specific molecule – the **substrate**; the **products** are the chemical substances that result from the enzyme's action.

gene expression and protein synthesis that alters physiological function of the target cells. Examples include receptors for:

- insulin – which initiates metabolic activity
- cytokines – which initiate inflammation
- growth factors – which initiate cell division.

18.9 Drugs that affect enzyme action

Drugs target enzymes in a range of ways that can be reversible (relatively transient) or irreversible (→ Box 18.17):

- **Competitive inhibition** of the enzyme takes place when a drug mimics the endogenous substrate and competes for the active site (→ Fig. 18.6b). The concentration of the drug is important for this kind of effect.
- **Non-competitive inhibition** takes place when the drug or agent binds to the enzyme molecule somewhere other than at the active site; the enzyme molecule can then no longer carry out its normal function because the drug has induced a change in shape.

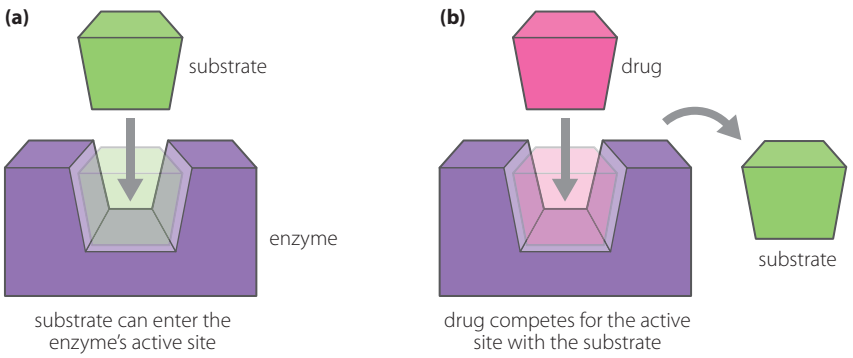

Fig. 18.6 (**a**) The shape of an enzyme's active site allows the substrate to bind precisely; (**b**) the drug displaces substrate molecules from the active site of the enzyme.

Examples of drugs that inhibit enzyme action

Anticholinesterases are a class of drugs that inhibit the enzyme acetylcholinesterase, which normally destroys the excitatory neurotransmitter acetylcholine in synapses (→ 9.4.4) and neuromuscular junctions (→ Fig. 4.22). Hence these drugs increase the concentration of acetylcholine within the nervous system. These drugs are often used:

- to reverse the effects of neuromuscular blockade after surgery and in the treatment of the autoimmune disorder myasthenia gravis
- to slow the cognitive decline in people who have Alzheimer's disease.

Anticholinesterases are associated with adverse effects on the digestive system including nausea, vomiting, diarrhoea and cramps. They may also interact with other drugs to slow the heart and lower blood pressure.

Angiotensin-converting enzyme (ACE) inhibitors act by stopping the production of angiotensin II. This leads to relaxation of blood vessels (vasodilatation), a fall in peripheral resistance and lowering of blood pressure, so they are used as antihypertensive agents.

Non-steroidal anti-inflammatory drugs (NSAIDs) are a chemically diverse group of drugs that all have the ability to inhibit cyclo-oxygenase which reversibly reduces the production of prostaglandins. This is why NSAIDs such as aspirin and ibuprofen are effective in reducing inflammation and pain.

Statins – 3, hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors – reduce the ability of hepatocytes (liver cells) to synthesise cholesterol. These drugs can be used to prevent adverse coronary events, e.g. myocardial infarction.

18.9.1 Drugs that affect coagulation of blood

Some drugs act directly on plasma proteins and an example of this type of drug is the group of anticoagulants – drugs that retard or inhibit the coagulation of the blood.

Haemostasis (ability of blood to clot) is an important aspect of cardiovascular homeostasis that ensures blood loss is prevented or minimised. **Thrombosis** is formation of a clot in a blood vessel (artery or vein) that arises from altered blood flow through a tissue and disease processes including narrowing or injury to the blood vessel wall. When this happens, the clot prevents normal blood flow, and organs such as heart, brain and lungs are particularly susceptible. Patients who are recovering from surgery or have chronic inflammatory disorders are prone to stasis of blood in circulation; a part of a thrombus (called an embolus) may break loose and enter the systemic circulation (→ Box 18.18).

Box 18.18 Haemostasis depends on enzymes in plasma which are activated at every step of the clotting cascade, so the function of anticoagulant drugs is to inhibit the enzymes.

Examples of anticoagulant drugs

Anticoagulant drugs are widely used to prevent thrombus (clot) formation and include the following:

- Clopidogrel and aspirin are antiplatelet drugs that make platelets less sticky. They inhibit platelet aggregation and stop platelet plugs from adhering to vessel walls.
- Heparin is a short-acting anticoagulant that prevents thrombus formation and thus inhibits the coagulation cascade. This is a preferred drug for pregnant women as it does not cross the placenta.
- Warfarin has a long duration of action and prevents the synthesis of vitamin K-dependent clotting factors. Its target is the enzyme that enables the vitamin to participate in the coagulation cascade.
- Thrombolytic (fibrinolytic) drugs such as alteplase, that form complexes with enzymes responsible for clot dissolution, are used to break down preformed clots after an infarct has happened; they are commonly known as 'clot busters'.

Coagulation monitoring is needed for people taking this group of drugs to establish and ensure the appropriate dose that avoids risk of haemorrhage, particularly when they are taken with some other drugs. Dietary issues, e.g. vitamin K intake, can affect their action.

18.10 Drugs that act at synapses and neuromuscular junctions

Action potentials (nerve impulses) cannot cross the physical gap between two neurons. Instead, information flows by means of neurotransmitters across a synapse – a small gap separating the two cells (→ 9.4.4).

Synapses comprise:

- the presynaptic ending, which is located at the end of an axon and contains cell organelles and vesicles with neurotransmitter molecules
- the synaptic cleft (space) into which the neurotransmitter molecules are secreted in response to an action potential

- a postsynaptic ending that has specific binding sites (**neuroreceptors**) for the neurotransmitter molecules – usually gated ion channels – in its membrane (➔ Fig. 18.7a).

Since synapses form the contact points between neurons and other cells, a drug can alter the way a synapse functions in many ways, but in general terms:

- **Agonist drugs** increase the effect of a given neurotransmitter at the synapse. They may achieve this effect by increasing the production of a given neurotransmitter, by mimicking the effect of the neurotransmitter, or inhibiting the removal of the neurotransmitter (➔ Fig. 18.7b).
- **Antagonist drugs** decrease the effect of the neurotransmitter. This can occur because production of the neurotransmitter is reduced, because the receptor site may be blocked by the antagonist, or removal of the neurotransmitter may be increased (➔ Fig. 18.7c).

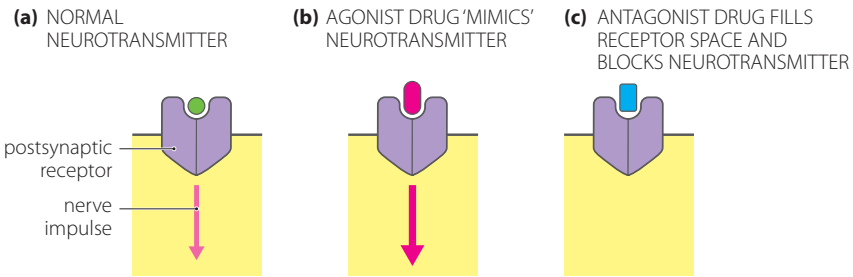

Fig. 18.7 How agonist and antagonist drugs act at synapses.

18.10.1 Examples of drugs that act at synaptic sites

- **Excitatory ion channel synapses**. Some drugs act at sodium channels that respond rapidly to neurotransmitters like acetylcholine, glutamate or aspartate. Binding of the ligand or drug alters the flow of the positive ions across the cell membrane, increasing the excitability of the neuron.
- **Inhibitory ion channel synapses**. Often these are chloride channels in the membrane that neurotransmitters – glycine or gamma-amino butyric acid (GABA) can bind to; when the channels are open, negative ions flow into the cell, causing hyperpolarisation and reducing the excitability of the neuron.
- **Non channel synapses**. When these are activated by neurotransmitters, they lead to the production of 'second messenger' molecules inside the cell (➔ Fig. 18.3). The cascade of intracellular responses can lead to slower, longer-lasting change(s) in cell activity or behaviour. Typical neurotransmitters that act at this type of synapse are noradrenaline, dopamine, serotonin, opioids, angiotensin and acetylcholine.

18.10.2 Examples of drugs that act at neuromuscular junctions

Neuromuscular junctions are a specialised form of synapse between the terminal of a motor neuron and the motor end-plate of a skeletal muscle. They are always excitatory and always depend on acetylcholine as the neurotransmitter. Depolarisation of the axon terminal triggers influx of

calcium and release of acetylcholine (→ Fig. 9.13) which diffuses across the synaptic cleft. Then it binds to a specific receptor on the surface of the muscle.

- **Neuromuscular blocking agents** are used by anaesthetists to relax skeletal muscles during surgical procedures or electroconvulsive therapy (ECT). Some – tubocurarine, pancuronium or vecuronium – are competitive antagonists that stop acetylcholine from binding to its receptors. Suxamethonium is a depolarising blocking agent because it binds to the acetylcholine receptor and triggers opening of ion channels, causing brief muscle fibre twitches before the muscle relaxes.
- **Muscarinic antagonists**, such as atropine and hyoscine, block the effects of acetylcholine that has been released from parasympathetic nerve endings in smooth muscles or glands, although they are variable in their sensitivity to the drugs.
- **Botulinum toxin (Botox)** prevents acetylcholine release and is produced by the anaerobic bacterium *Clostridium botulinum*, which can cause food poisoning and paralysis. Low doses of the toxin are sometimes used in the management of urinary incontinence in people with spinal injuries.

18.10.3 Drugs that affect the termination of signals at synapses and neuromuscular junctions

After a post-synaptic neuron has been stimulated or inhibited by binding with a specific neurotransmitter molecule, the signal needs to be switched off and this can be achieved in several ways:

- **Presynaptic terminals** stop secreting neurotransmitter molecules into the synaptic cleft because action potentials in its axon cease. The concentration of neurotransmitter falls as it diffuses away from the local area.
- **Neurotransmitter molecules are degraded** (broken down) by enzyme action in the synaptic cleft so they are inactivated and no longer have an effect, e.g. by the enzymes acetylcholinesterase and monoamine oxidase (→ Fig. 18.8).

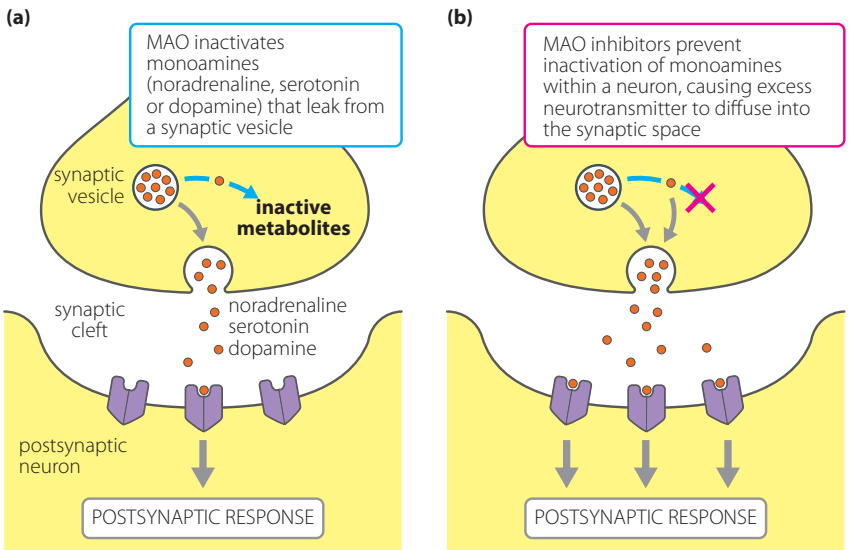

Fig.18.8 Monoamine oxidase is an enzyme that degrades monoamine neurotransmitters: (**a**) normal monoamine transmission; (**b**) action of monoamine oxidase inhibitors.

- **neurotransmitter molecules are taken back** up into the presynaptic neuron so they can be recycled. Since transport (carrier) proteins play an important part in moving neurotransmitters across cell membranes, they are increasingly becoming target molecules for drug actions
- **ion channels and receptors become desensitised** to the action of the neurotransmitter; thus signal is limited.

Examples of drugs that affect termination of signals at synapses and neuromuscular junctions

- **Selective serotonin reuptake inhibitors (SSRIs)** target protein molecules that are embedded in presynaptic membranes of serotonergic neurons in the central nervous system. These transporters function to pump serotonin molecules from the synaptic cleft back into the presynaptic cells and are inhibited by drugs such as fluoxetine. This leads to elevated concentrations of the neurotransmitter and enhanced action (➔ Fig. 18.9).
- **Tricyclic antidepressants** block reuptake transporters for serotonin and noradrenaline, while some act as antagonists for binding of several neurotransmitters. Although this class of drugs is effective, it has increasingly been replaced by newer antidepressants with an improved safety and fewer adverse side-effects.
- **Monoamine oxidase inhibitors (MAOIs)** inhibit the activity of the enzyme that degrades noradrenaline, dopamine and serotonin. They are best known as therapeutic agents for depression, panic disorder and social phobia as well as Parkinson's disease. However, they can have severe drug and food interactions.

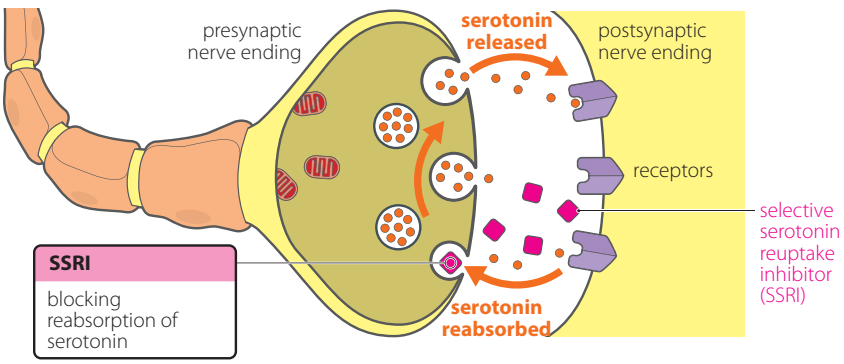

Fig. 18.9 Action of selective serotonin reuptake inhibitors.

18.10.4 Examples of antipsychotic drugs

Neuroleptic drugs (neuroleptic agents) are used to help control symptoms of schizophrenia and other psychotic disorders. This group of drugs has a wide variety of chemical structures but they are all antagonists at dopamine receptors. In particular, the neuroleptic drugs have a high affinity for subtype D2. The symptoms of schizophrenia fall into two main categories:

- positive symptoms including hallucinations, delusions and disordered thoughts
- negative symptoms including social withdrawal, poverty of speech, attention deficit.

The **dopaminergic pathways** and D2 receptors are involved in pre- and post-synaptic inhibition in the **limbic cortex** (➔ 9.3.4) which function in mood and emotions, so blockade of these receptors is the main therapeutic

strategy. The main drug treatments tend to have greater effect on positive symptoms; negative symptoms are very difficult to manage.

Neuroleptic drugs also block dopamine receptors in other parts of the brain, which frequently causes distressing and disabling side-effects:

- movement disorders (known as **extrapyramidal effects**), e.g. parkinsonism, restlessness
- **autonomic effects** including dry mouth, constipation and postural hypotension
- **endocrine effects** that result in raised levels of prolactin
- **weight gain** which can be significant and is associated with type 2 diabetes.

18.10.5 Analgesics

Analgesics relieve pain. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. When cells are damaged, pro-inflammatory chemical mediators (prostaglandins, bradykinin, ATP) are released and stimulate nociceptors (→ 9.9.1). Information relating to intensity is then transmitted by primary neurons of the pain pathway to the substantia gelatinosa in the dorsal horn of the spinal cord. Ascending spinothalamic fibres project to the brainstem and thalamus and then to the cerebral cortex where the signals are interpreted as pain (→ Fig. 9.22). A large number of neurotransmitters and other chemical mediators play a part in the process.

Common analgesics

Analgesia means loss of sensation of pain. A wide range of common analgesics and techniques are used to treat pain of different types and levels, affecting different parts of the pain pathway based on receptor targets. There are five commonly-used analgesics:

- **Non-steroidal anti-inflammatory drugs (NSAIDs)** such as ibuprofen reduce the production of prostaglandins at the site of the injury. They are selective inhibitors (blockers) of cyclo-oxygenase (COX) pathway enzymes and are used for mild to moderate pain (→ 18.9). These drugs also lower body temperature (i.e. they are anti-pyretic). Gastrointestinal side-effects can be quite troublesome, e.g. peptic ulcers. Aspirin was the first drug in this category to be discovered.
- **Paracetamol** is not thought to affect cyclo-oxygenase pathways but also relieves pain and fever.
- **Local anaesthetics** block sodium channels in neuronal membranes so the cells cannot depolarise, providing a good level of analgesia, e.g. cocaine, procaine or lignocaine (→ 18.8.2). **Epidural injection** of local anaesthetic into the spinal space blocks the transmission of pain signals from spinal cord to the brain. Unwanted effects from this group of drugs generally only arise if the drug enters the CNS.
- **Antidepressants can be used as analgesics** if they relieve depression that is giving rise to pain, e.g. amitriptyline.
- **Opiates** such as codeine, morphine and fentanyl bind to opioid receptor sites within the CNS and act as agonists for the endogenous analgesia system – sometimes known as 'endorphins'. There are a variety of **opioid receptors**, which modulate pain by binding in ways that result in different effects (→ Box 18.19). Although the pain signals are not perceived, the person may experience euphoria.

Box 18.19 The opiates are controlled substances; they can have serious side-effects including respiratory depression, bradycardia, constipation and vomiting. Their action can be reversed by naloxone.

18.11 Drugs that suppress gene function

Many drugs act as suppressors of **gene function** including antibiotics, fungicides, antimalarials, antivirals and chemotherapeutic agents.

Gene function may be suppressed in several steps of protein synthesis or inhibition of nucleic acid biosynthesis. Many substances which inhibit nucleic acid biosynthesis are very toxic since the drugs are not very selective in their action.

18.11.1 Chemotherapy agents

Cancer is a disease process that involves development and reproduction of abnormal cells so the goal of chemotherapy (antineoplastic therapy) is to kill scattered tumour cells after surgery and radiation to make sure that all cancerous cells are eliminated.

Chemotherapy agents are generally divided into two main groups:
- **cell-cycle specific** that act during M phase of cell division (➔ Fig 13.4)
- **cell-cycle non-specific** that are cytotoxic at any stage of the cell cycle.

Examples are:
- alkylating drugs (e.g. vincristine) that bind irreversibly with DNA, RNA and proteins so that mitosis (➔ 13.4.2) is inhibited
- antitumour antibiotics which slip between neighbouring base pairs of DNA; this group of drugs are not like the antibiotics for infection, but they interfere with DNA and stop cancer cells from growing
- antimetabolites which inhibit enzymes that are essential for synthesis of DNA, RNA and proteins
- topoisomerase inhibitors that interrupt DNA replication, resulting in cancer cell death
- monoclonal antibodies (e.g. trastuzumab) that target receptors for growth factors
- hormone antagonists (e.g. tamoxifen) target receptors on tumour cells that depend on hormones such as oestrogen for their growth.

It is important to note that most chemotherapy agents are not selective and cannot distinguish between cancer cells and normal cells; this is why they tend to be very toxic drugs causing nausea, vomiting, hair loss (alopecia), bone marrow suppression – anaemia and thrombocytopenia – and skin disturbances. They are not usually used during pregnancy since they are teratogenic, causing foetal malformations. Combination drug regimens are very specific, as are dosing schedules, requiring specialist teams.

18.11.2 Antibiotics

An important quality for an antimicrobial drug is **selective toxicity**, meaning that it selectively kills or inhibits the growth of microbial targets while causing minimal or no harm to the host (➔ Box 18.20). Most antimicrobial drugs currently in clinical use are antibacterial because bacterial cells provide a greater variety of targets for selective toxicity, in comparison to fungi, parasites and viruses. Each class of antibacterial drugs has a unique mode of action (the way in which a drug affects microbes at the cellular level).

Box 18.20 The "antibiotic era" began in the 20th century with early antibiotics [anti= against; biotic= life] such as penicillin and sulphonamides.

18.11.3 Antibacterial drugs

Since ancient times, people have been using moulds, soil and plants as remedies to treat illness and infectious diseases, but today's health professionals understand that efficacy of early treatments was due to the properties of active chemical agents.

Although the importance of the immune system, good lifestyle management and public health measures should not be underestimated, there are still many disease conditions that can only be addressed by antimicrobial therapy. Today, therefore, the term **antibiotic** refers to a substance that is produced by a microorganism or a similar substance produced synthetically and which in low concentrations kills microorganisms or inhibits their growth.

Bacterial cells have many chemical differences from human cells, so anti-bacterial drugs and antibiotic agents are often non-toxic (or not too toxic) to humans. The effect of antibiotics is described as either:

- **bactericidal** – an agent that destroys the causative microorganism by killing it
- **bacteriostatic** – an agent that inhibits the growth of the microorganism and host defence mechanisms that are involved in the final elimination process.

Antibiotics can be:

- **narrow spectrum** – if they are effective against a small group of bacteria; would be useful for infections caused by a single pathogen, e.g. a skin infection caused by staphylococcus
- **broad spectrum** – if they are effective against a wide range of pathogens, having activity against both Gram-positive bacteria and Gram-negative bacteria, e.g. might be indicated against a polymicrobial infection, such as an intra-abdominal anaerobic infection (→ Box 18.21).

Box 18.21 There are two major classifications of bacteria:
Gram-positive bacteria have cytoplasm that is surrounded by a membrane and a tough, rigid mesh called the cell wall.
Gram-negative bacteria have a thin cell wall that is surrounded by an additional, protective lipid layer called the outer membrane (OM), which prevents many substances from entering the cytoplasm; this structure has channels that allow entry of substances including drugs.

18.11.4 Antibiotic therapy

Guiding principles of antibiotic therapy are complex because different antibiotics have different chemical structures, mode of action and affinity to the bacterial target sites, but most act by:

- **inhibiting synthesis of bacterial cell walls.** Bacterial cell walls are made of sugar polymers known as peptidoglycan which is essential for their survival, so this is the most common mode of action of antimicrobials (→ Fig. 18.10). Examples of antibiotics that selectively target cell walls of actively growing bacteria are cephalosporins and penicillin which share a common chemical feature of a β-lactam ring structure. They lead to lysis of the bacterial cell.
- **disrupting bacterial cell membrane functions.** When membranes are damaged, regulation of the passage of substances in and out of cells is disrupted and an example of an antibiotic that acts to do this is colistin. However, plasma membranes are found in both prokaryotic (bacterial) and eukaryotic (human) cells, so this class of agents is poorly selective and can be toxic so has limited clinical use (→ Box 18.22).
- **stopping protein synthesis by the bacteria.** By targeting and interfering with the function of bacterial ribosomes, some antibacterial agents disrupt normal metabolic processes, leading to cell death. Examples include aminoglycosides, macrolides, chloramphenicol and tetracyclines.

Box 18.22 An infection arises when pathogenic (harmful) bacteria grow in an uncontrolled way anywhere in the body so that they and their toxins cause damage to cells. The concept of **selective toxicity** is applied to describe the action of an antibacterial drug which targets the pathogens but not the person who is their host.

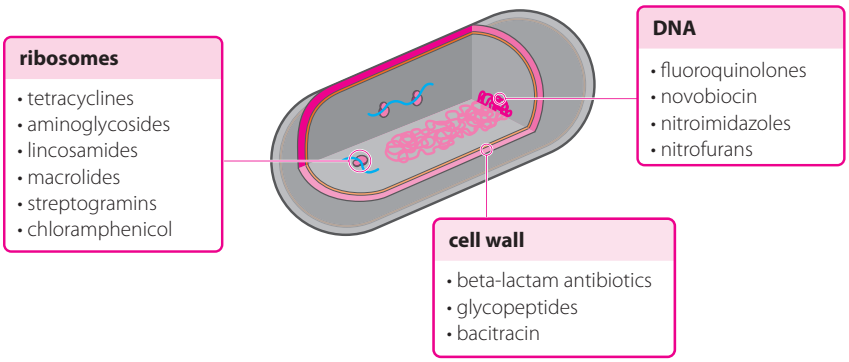

Fig. 18.10 Major targets of common antimicrobial agents.

- **inhibiting nucleic acid synthesis.** DNA and RNA are essential for bacterial reproduction, so some antibiotics interfere with nucleic acid synthesis, which means that they cannot reproduce. Examples from this group include quinolones, metronizadole and rifampicin.
- **inhibition of metabolic pathways.** Sulphonamides and trimethoprim inhibit a bacterial enzyme that is essential for the synthesis of folate and DNA. Human cells can absorb folate from the diet, but bacterial cells cannot absorb it and depend on synthesis. By selectively targeting the bacterial cells, these drugs stop the growth of bacteria.

18.11.5 Targeted or empirical therapy

Antibiotic therapy is either:

- **targeted** antiobiotic therapy – therapy initiated after bacterial culture and a susceptibility report has been produced
- **empirical** antibiotic therapy – starting antibiotic therapy that targets the most likely causative microorganisms. It is used in cases of potentially life-threatening infections or sepsis, e.g. meningitis, pneumonia, surgical site infections, dysentery or urinary tract infections.

Selecting an antibiotic that will optimally treat an infection, while minimising adverse effects and development of antibiotic resistance, is a very complex task for prescribers (→ Box 18.23). Ideally, microbiological testing is carried out (→ 17.6) to determine the:

- species of invading bacterial pathogen
- susceptibility of the pathogen to antibiotic
- drug attributes – its pharmacodynamics, pharmacokinetics, tissue distribution. Prescribers must take account of the route for delivery of the antibacterial agent and its absorption by the body, as well as common side-effects – rashes, allergies and hypersensitivities, nephrotoxicity and hepatotoxicity
- host characteristics such as age or immune status. For example, some antibiotics are contraindicated for specific groups of patients, e.g. children, pregnant women or lactating mothers
- interactions with other medications.

Box 18.23 Certain sites are difficult to reach by antibiotics and require the use of higher/more frequent doses, longer duration of therapy, combinations of antibiotics, and/or the use of antibiotics that cross the blood–brain barrier.

18.12 Antimicrobial resistance

Infectious diseases remain a major cause of death across the world. This is because of the appearance of antimicrobial (antibiotic) resistance, the re-emergence of diseases once controlled by antibiotics and the emergence of new infectious agents. A growing number of infections – tuberculosis, pneumonia, gonorrhoea, salmonellosis – are becoming more difficult to treat, and misuse of antibiotics in people and animals is accelerating the process (→ Box 18.24).

When a strain of bacteria becomes resistant to the drugs that are used therapeutically to fight it, it becomes difficult – maybe impossible – to treat. Bacteria that are resistant to antibiotics are more likely to survive and multiply, passing on their genes for antibiotic resistance to the next generation. Antibiotic resistance is one of the greatest threats to global health, food security and development today.

Improved understanding of the mechanisms by which antimicrobial resistance develops can help healthcare professionals regarding the use of different antibiotics in different situations and settings.

Hospitals are frequently affected by outbreaks of antibiotic-resistant strains of bacteria because:
- there are large numbers of people who may be carrying pathogenic organisms
- inpatients may have weakened immune systems and are thus particularly vulnerable to infection
- hospitals rely on strict hygiene practices and these may not always be adhered to
- antibiotics are being used heavily, e.g. before or following surgical procedures
- hospital waste is more likely to contain antibiotics and resistant bacteria.

Contaminated environments may provide more favourable conditions for the survival of resistant strains of bacteria because of:
- human or animal waste that contains antibiotics that the person or animal has been treated with
- antibiotics that were used to treat and prevent crop-plant disease
- waste from pharmaceutical plants that are making antibiotics
- water courses that harbour 'reservoirs' of resistant bacteria from swimmers, surfers and fish farms
- soil in fields that were fertilised with infected manure or irrigated with infected water.

Box 18.24 Antimicrobial resistance (AMR) is the ability of microorganisms, e.g. bacteria, viruses and some parasites, to stop an antimicrobial agent (such as antibiotics, antivirals and antimalarials) from working against it. As a result, standard treatments become ineffective; infections persist and may spread to other people. Antibiotic resistance leads to longer hospital stays, higher medical costs and increased mortality.

18.12.1 Preventing the the spread of antibiotic resistance

To prevent the spread of antibiotic resistance, health professionals can:
- talk to patients about how to take antibiotics correctly, antibiotic resistance, and the dangers of misuse
- ensure that hands, instruments and the environment are clean
- only prescribe and dispense antibiotics when they are needed, according to current guidelines
- talk to patients about preventing infections, e.g. vaccination, hand washing, safer sex, and covering nose and mouth when sneezing
- report antibiotic-resistant infections to infection surveillance and control teams.

18.13 Therapeutic window

The goal of all drug therapy is to select a dose that lies within the therapeutic range for the individual and avoid doses that are toxic, so the concept of the therapeutic window can be useful for healthcare professionals.

The **therapeutic window** is defined as the range of dosages of a drug or agent that produces a therapeutic response without causing significant adverse effects in the person. The window lies between measurable variables related to exposure to a substance, e.g.:

- the minimum effective concentration (MEC)
- the minimum toxic concentration (MTC).

The therapeutic window is also sometimes called the **safety window** for a given substance and is quantified by the **therapeutic index** (→ 18.13.1). A person's level of exposure to the effects of any substance will be determined by factors such as food intake, body mass, other drugs (medicines) they may be taking, liver function, genomic profile, pregnancy and breastfeeding.

Some drugs have a particularly narrow therapeutic range that requires careful patient monitoring and regular review, e.g.:

- lithium which is taken by people with bipolar disorders
- warfarin (anticoagulant drug)
- phenytoin (anti-epileptic drug)
- digoxin (cardiac glycoside) for people with atrial fibrillation or heart failure
- amiodarone (cardiac anti-arrhythmia drug)
- sunitinib (anticancer drug).

Box 18.25 The **therapeutic index** must always be taken into account when healthcare professionals are making decisions about the dose of a drug which is to be given to an individual.

18.13.1 Therapeutic index

The term therapeutic index describes the relationship between the dose of a drug that has a therapeutic effect and the dosage that could be lethal. This term is used during research studies and trials to establish dosage levels for testing (→ Box 18.25).

18.13.2 Drug interactions and complex needs

Many drugs are formulated in varying potency and duration of action but drug development is a long process involving many tests and clinical trials – a process that can take many years. However, therapeutic properties become undesired side-effects in nearly all other clinical instances. Adverse effects force doctors and health professionals to exercise caution and pay attention to side-effects when prescribing and dispensing any class of agents.

18.14 Adverse reactions to drugs

The perfect drug does not exist because its desired therapeutic effect has the potential to be accompanied by undesirable effects (→ Box 18.26). The properties of any drug determine the effects it will produce, but all drugs target the molecular biology of cells and influence their function and the effects on the individual. Since undesired effects of drugs are often dose-related, the terms provide a means of identifying the potential severity of the various types of undesired effects of substances in the body.

- **Side-effects** such as dry mouth or sleepiness are undesirable and may commonly be experienced as more of a nuisance than harmful. More likely to occur at low doses, their possibility needs to be explained to the person who is taking a medication.

Box 18.26 Digoxin is extracted from a plant – *Digitalis lanata* – and has a therapeutic effect that improves cardiac contractility and prolongs the time taken for the cardiac impulse to travel through the heart. However, adverse effects include vomiting, diarrhoea and a variety of arrhythmias. More recently specific anti-digoxin antibodies have been introduced for management of severe digoxin toxicity.

- **Adverse effects** may cause harm to the individual who is taking the drugs, e.g. persistent diarrhoea or constipation, vomiting, disturbances of the CNS or damage to vital organs such as heart, kidney or liver. Adverse effects include predictable, dose-related effects caused by excess of the drug's pharmacological effect, e.g.:
  - hypoglycaemia in a person who is insulin-dependent
  - bleeding in a person taking the anticoagulant warfarin
  - respiratory depression with morphine.

Often these effects are caused by incorrect dosage or altered pharmacokinetics because of a person's age, renal impairment, genomic profile or interactions with other drugs.

- **Unpredictable effects** that are not necessarily dose-related are a rarer phenomenon, e.g. **anaphylaxis or other hypersensitivity** that involves the immune system and complement activation. Such responses include rashes, itchy skin reactions, respiratory difficulties or hypotension.
- **Teratogenic effects** can occur when drugs cross the placenta so, if possible, drugs should be avoided during pregnancy. Some drugs have the potential to increase incidence of abnormal foetal development, often during the first trimester, which could lead to congenital (birth) defects. These drugs include thalidomide, alcohol causing foetal alcohol syndrome, valproate contributing to neural tube defects, anticonvulsants, and tetracycline causing bone growth defects.
- **Carcinogenic effects** caused by drugs that cause tumour growth.
- **Idiosyncratic effects** that occur when an individual responds to a drug in a very unexpected or unusual way.
- **Toxic effects**. All drugs will act as poisons if taken in excess. The consequences of toxicity usually imply poisoning, and the drug should be stopped. When the consequences are extremely harmful or life-threatening, the affected individual may require nursing and medical support.

18.15 Toxicology

Toxicology is the branch of pharmacology which deals with poisons (toxins) which are substances that are capable of killing or injuring a person even when ingested or absorbed in small amounts. Death results when the extent and duration of body dysfunction has gone so far that treatment no longer works and recovery become impossible.

Poisons

Poison is a relative term since the lethal dose depends on the substance, e.g. strychnine or cyanide are very highly toxic. Many drugs and medications can be useful and therapeutic when used in appropriate dosages, but can be lethal when taken in excess. Thus there is a vast number of potential poisons.

People vary according to their sensitivity to a toxin, which could depend on its source and chemical properties. They also vary in the signs and symptoms that a poisonous substance produces. Poisoning can be:

- **acute** – a single dose leads to onset of symptoms that run a short course, e.g. cyanide or ricin
- **chronic** – repeated exposures to small doses of substances that may accumulate in the body, e.g. mercury compounds during occupational exposure
- **accidental** – substances found in or around people's homes, mistaking someone else's tablets for sweets, or eating poisonous berries
- **deliberate** – overdose of sedatives or 'social' drugs is self-poisoning in suicide attempts; the use of poison gases in warfare contravenes international law.

Key points

1. Pharmacology examines the composition, uses and effect of drugs on the human body.
2. Pharmacology combines aspects of chemistry, physiology and pathology because every drug or medication changes the biochemistry of the body.
3. Pharmacokinetics examines the ways in which the body processes drugs.
4. Bioavailability relates to the proportion of administered drug that reaches the circulation.
5. Pharmacodynamics describes the physiological and biochemical effects of drugs on the body.
6. Examples of some important classes of agents used in healthcare settings are included to illustrate pharmacological concepts.