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# MEDICAL PHARMACOLOGY & THERAPEUTICS

Derek G. Waller | Anthony P. Sampson

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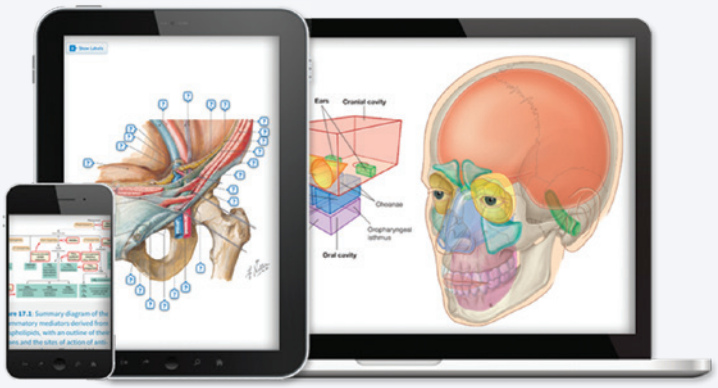

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Fifth Edition

# MEDICAL PHARMACOLOGY & THERAPEUTICS

# Dedication

*To our families*

Fifth Edition

# MEDICAL PHARMACOLOGY & THERAPEUTICS


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Edinburgh London New York Oxford Philadelphia St Louis Sydney Toronto 2018

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First edition 2001
Second edition 2005
Third edition 2010
Fourth edition 2014
Fifth edition 2018



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**ISBN:** 978-0-7020-7167-6
Printed in China
Last digit is the print number: 9 8 7 6 5 4 3 2 1

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# Preface

The fifth edition of *Medical Pharmacology and Therapeutics* has been extensively revised and updated while preserving the popular approach of the fourth edition. We particularly wish to acknowledge here the contributions made to previous editions of this book by Emeritus Professor Andrew Renwick OBE BSc PhD DSc and Dr Keith Hillier BSc PhD DSc, Senior Lecturer in Pharmacology, formerly our colleagues in the University of Southampton Faculty of Medicine. As before, a disease-based approach has been taken to explain clinical pharmacology and therapeutics and the principles of drug use for the management of common diseases. *Medical Pharmacology and Therapeutics* provides key information on basic pharmacology and other relevant disciplines sufficient to underpin the clinical context. It provides information suitable for all healthcare professionals who require a sound knowledge of the basic science and clinical applications of drugs.

The text is structured to reflect the ways that drugs are used in clinical practice. The chapters covering generic concepts in pharmacology and therapeutics include sections on how drugs work at a cellular level, drug metabolism and pharmacokinetics, pharmacogenetics, drug development and drug toxicity. The basic principles of prescribing have been emphasized and new information provided on preparing for the Prescribing Safety Assessment (PSA) in the UK. New sections have been included on pharmacovigilance, on so-called 'legal highs' and in all other areas, and the sections on clinical management have been thoroughly revised and updated.

Each chapter in this fifth edition retains the following key features:

- An up-to-date and succinct explanation of the major pathogenic mechanisms of disease and consequent clinical symptoms and signs, helping the reader to put into context the actions of drugs and the consequences of their therapeutic use.
- A structured approach to the principles of disease management, outlining core principles of drug choice and planning a therapeutic regimen for many common diseases.
- A comprehensive review of major drug classes relevant to the disease in question. Basic pharmacology is described with clear identification of the molecular targets, clinical characteristics, important pharmacokinetic properties and unwanted effects associated with individual drug classes. Example drugs are used to illustrate the common pharmacological characteristics of their class and to introduce the reader to drugs currently in widespread clinical use.
- To complement the information provided within each chapter, a drug compendium is included describing the main characteristics of all drugs in each class listed in the British National Formulary.
- A revised section of self-assessment questions for learning and revision of the concepts and content in each chapter, including one best answer (OBA), extended matching items (EMI), true-false and case-based questions.

It is our intention that the fifth edition of this book will encourage readers to develop a deeper understanding of the principles of drug usage that will help them to become safe and effective prescribers and to carry out basic and clinical research and to teach. As medical science advances these principles should underpin the life-long learning essential for the maintenance of these skills.

DGW
APS

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# Drug dosage and nomenclature

## DRUG NOMENCLATURE

In the past, the nonproprietary (generic) names of some drugs have varied from country to country, leading to potential confusion. Progressively, international agreement has been reached to rationalise these variations in names and a single recommended International Non-proprietary Name (INN) given to all drugs. Where the previously given British Approved Name (BAN) and the INN have differed, the INN is now the accepted name and is used throughout this book.

A special case has been made for two medicinal substances: adrenaline (INN: epinephrine) and noradrenaline (INN: norepinephrine). Because of the clinical importance of these substances and the widespread European use and understanding of the terms *adrenaline* and *noradrenaline*, manufacturers have been asked to continue to dual-label products adrenaline (epinephrine) and noradrenaline (norepinephrine). In this book, where the use of these agents as administered drugs is being described, dual names are given. In keeping with European convention, however, adrenaline and noradrenaline alone are used when referring to the physiological effects of the naturally occurring substances.

## DRUG DOSAGES

Medical knowledge is constantly changing. As new information becomes available, changes in treatment, procedures, equipment and the use of drugs become necessary. The authors and the publishers have taken care to ensure that the information given in the text is accurate and up to date. However, readers are strongly advised to confirm that the information, especially with regard to drug usage, complies with the latest legislation and standards of practice.

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# 1

# General principles

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# 1 Principles of pharmacology and mechanisms of drug action



## STUDYING PHARMACOLOGY

Drugs are defined as active substances administered to prevent, diagnose or treat disease, to alleviate pain and suffering, or to extend life. Pharmacology is the study of the effects of drugs on biological systems, with medical (or clinical) pharmacology concerned with the drugs that doctors, and some other healthcare professionals, prescribe for their patients. The prescribing of drugs has a central role in therapeutics, and gaining a good knowledge of pharmacology is essential for health professionals to become safe and effective prescribers.

Drugs may be chemically synthesised or purified from natural sources with or without further modification, but their development and clinical use are based on rational evidence of efficacy and safety derived from controlled experiments and randomised clinical trials. Drugs can be contrasted with placebos (*placebo* is Latin for 'I will please'), defined as inactive substances administered as though they are drugs, but which have no therapeutic effects other than potentially pleasing the patient, providing a sense of security and progress. Pharmacology evolved on the principle of studying known quantities of purified, active substances to identify their specific mechanisms of action and to quantify their effects in a reproducible manner, usually compared with a placebo or other control substance.

Much of the success of modern medicine is based on pharmacological science and its contribution to the development of safe and effective pharmaceuticals. This book is confined to pharmacology as it relates to human medicine and aims to develop knowledge and understanding of medical pharmacology and its application to therapeutics. The objectives of learning about medical pharmacology and therapeutics are:

- to understand the ways that drugs work to affect human systems, as a basis for safe and effective prescribing;
- to appreciate that pharmacology must be understood in parallel with related biological and clinical sciences, including biochemistry, physiology and pathology;
- to develop numerical skills for calculating drug doses and dilutions, and to enable accurate comparison of the relative benefits and risks of different drugs;
- to comprehend and participate in pharmacological research advancing the better treatment of patients.

The answer to the frequently asked question 'What do I need to know?' will depend upon the individual requirements of the programme of study being undertaken and the examinations that will be taken. The depth and type of

knowledge required in different areas and topics will vary when progressing through the programme; for example, early in the course it may be important to know whether a drug has a narrow safety margin between its wanted and unwanted effects, and in the later years this may translate into detailed knowledge of how the drug's effects are monitored in clinical use. Personal enthusiasm for medical pharmacology is important and should be driven by the recognition that prescribing medicines is the most common intervention doctors (and increasingly other health professionals) use to improve the health of their patients.

## FINDING DRUG INFORMATION

Learning about medical pharmacology is best approached using a variety of resources in a range of learning scenarios and preferably in the context of basic science and therapeutics, not from memorising lists of drug names. The following provides a useful structure to organise the types of information that you should aim to encounter:

- the nonproprietary (*generic*) drug name (not the *proprietary* or *trade name*);
- the *class or group* to which the drug belongs;
- the way the drug works (its *mechanism of action* and its *clinical effects*), usually shared to variable extents by other drugs in the same class;
- the main clinical reasons for using the drug (its *indications*);
- any reasons why the drug should not be used in a particular situation (its *contraindications*);
- whether the drug is a *prescription-only medicine* (PoM) or is available without prescription (over-the-counter [OTC]);
- how the drug is given (*routes of administration*);
- how its effects are quantified and its doses modified if necessary (*drug monitoring*);
- how the drug is absorbed, distributed, metabolised and excreted (ADME; its *pharmacokinetics*), particularly where these show unusual characteristics;
- the drug's *unwanted effects*, including any interactions with other drugs or foods;
- whether there are nonpharmacological treatments that are effective alternatives to drug treatment or will complement the effect of the drug.

The ***Appendix*** at the end of this chapter provides a formulary of core members of each major drug class to give students in the early stages of training a manageable list of the drugs most likely to be encountered in clinical practice. At the end of later chapters, the ***Compendium*** provides a classified listing and key characteristics of those drugs discussed within the main text of each chapter and also other drugs listed in the corresponding section of the *British National Formulary* (BNF).

The BNF (www.evidence.nhs.uk) contains monographs for nearly all drugs licensed for use in the United Kingdom and is the key drug reference for UK prescribers. Students should become familiar at an early stage with using the BNF for reference. More detailed information on individual drugs (the Summary of Product Characteristics [SPC]), patient information leaflets (PIL) and contact details for pharmaceutical companies is available from the electronic Medicines Compendium (eMC; www.medicines.org.uk/emc/).

# RECEPTORS AND RECEPTOR-MEDIATED MECHANISMS

Pharmacology describes how the physical interaction of drug molecules with their macromolecular targets ('receptors') modifies biochemical, immunological, physiological and pathological processes to generate desired responses in cells, tissues and organs. Drugs have been designed to interact with many different types of macromolecules that evolved to facilitate endogenous signalling between cells, tissue and organs, or to play key roles in the normal cellular and physiological processes that maintain controlled conditions (homeostasis). Drugs may also target macromolecules produced by pathogens, including viruses and bacteria. While the term 'receptor' was originally applied in pharmacology to describe any such drug target, more commonly a receptor is now defined in biochemical terms as a molecule on the surface of a cell (or inside it) that receives an external signal and produces some type of cellular response.

The function of such a receptor can be divided typically into three main stages:

1. **The generation of a biological signal.** Homeostasis is maintained by communication between cells, tissues and organs to optimise bodily functions and responses to external changes. Communication is usually by signals in the form of chemical messengers, including neurotransmitter molecules, local mediators or endocrine hormones. The signal molecule is termed a *ligand*, because it ligates (ties) to the specialised cellular macromolecule. The cellular macromolecule is a *receptor* because it receives the ligand.
2. **Cellular recognition sites (receptors).** The signal is recognised by responding cells by its interaction with a site of action, binding site or receptor, which may be in the cell membrane, the cytoplasm or the nucleus. Receptors in the cell membrane react with extracellular ligands that cannot readily cross the cell membrane (such as peptides). Receptors in the cytoplasm often react with lipid-soluble ligands that can cross the cell membrane.
3. **Cellular changes.** Interaction of the signal and its site of action in responding cells results in functional changes within the cell that give rise to an appropriate biochemical or physiological response to the original homeostatic stimulus. This response may be cell division, a change in cellular metabolic activity or the production of substances that are exported from the cell.

Each of these three stages provides important targets for drug action, and this chapter will outline the principles underlying drug action mainly in stages 2 and 3.

## ACTIONS OF DRUGS AT BINDING SITES (RECEPTORS)

For very many drugs, the first step in producing a biological effect is by interaction of the drug with a receptor, either on the cell membrane or inside the cell, and it is this binding that triggers the cellular response. Drugs may be designed to mimic, modify or block the actions of endogenous ligands at that receptor. The classified list of receptors at the end of this chapter shows that cell-membrane and cytosolic receptors

tend to occur in different families (receptor types), reflecting their evolution from common ancestors. Within any one family of receptors, different receptor subtypes have evolved to facilitate increasingly specific signalling and distinct biological effects. As might be expected, different receptor families have different characteristics, but subtypes within each family retain common family traits.

In pharmacology, the perfect drug would be one that binds only to one type or subtype of receptor and consistently produces only the desired biological effect without the unwanted effects that can occur when drugs bind to a related receptor. Although this ideal is impossible to attain, it has proved possible to develop drugs that bind avidly to their target receptor to produce their desired effect and have very much less (but not zero) ability to bind to other receptors, even ones within the same family, which might produce unwanted effects.

Where a drug binds to one type of receptor in preference to another, it is said to show *selectivity of binding* or *selectivity of drug action*. Selectivity is never absolute but is high with some drugs and lower with others. A drug with a high degree of selectivity is likely to show a greater difference between the dose required for its biological action and the dose that produces unwanted actions at other receptor types. Even a highly selective drug may produce unwanted effects if its target receptors are also found in tissues and organs other than those in which the drug is intended to produce its therapeutic effect.

## MAJOR TYPES OF RECEPTORS

Despite the great structural diversity of drug molecules, most act on the following major types of receptors to bring about their pharmacological effects:

- **Transmembrane ion channels.** These control the passage of ions across membranes and are widely distributed.
- **Seven-transmembrane (7TM) (heptahelical) receptors.** This is a large family of receptors, most of which signal via guanine nucleotide-binding proteins (G-proteins). Following activation by a ligand, second messenger substances are formed inside the cell, which can bring about cellular molecular changes, including the opening of transmembrane ion channels.
- **Enzyme-linked transmembrane receptors.** This is a family of transmembrane receptors with an integral or associated enzymic component, such as a kinase or phosphatase. Activation of these enzymes produces changes in cells by phosphorylating or dephosphorylating intracellular proteins, including the receptor itself, thereby altering their activity.
- **Intracellular (nuclear) receptors.** These receptors are found in the nucleus or translocate to the nucleus from the cytosol to modify gene transcription and the expression of specific cellular proteins.

## Transmembrane ion channels

Transmembrane ion channels that create pores across phospholipid membranes are ubiquitous and allow the transport of ions into and out of cells. The intracellular concentrations of ions are controlled by a combination of two types of ion channel:

- ion pumps and transporters, which transport specific ions from one side of the membrane to the other in an energy-dependent manner, usually against their concentration gradient;
- ion channels, which open to allow the selective, passive transfer of ions down their concentration gradients.

Based on concentration gradients across the cell membrane:

- both $Na^+$ and $Ca^{2+}$ ions will diffuse into the cell if their channels are open, making the electrical potential of the cytosol more positive and causing depolarisation of excitable tissues;
- $K^+$ ions will diffuse out of the cell, making the electrical potential of the cytosol more negative and inhibiting depolarisation;
- $Cl^-$ ions will diffuse into the cell, making the cytosol more negative and inhibiting depolarisation.

The two major families of ion channel are the *ligand-gated ion channels* (*LGICs*) and the *voltage-gated ion channels* (*VGICs*; also called *ionotropic receptors*). LGICs are opened by the binding of a ligand, such as the neurotransmitter acetylcholine, to an extracellular part of the channel. VGICs in contrast are opened at particular membrane potentials by voltage-sensing segments of the channel. Both channel types can be targets for drug action. Both LGICs and VGICs can control the movement of a specific ion, but a single type of ion may flow through more than one type of channel, including both LGIC and VGIC types. This evolutionary complexity can be seen in the example of the multiple types of $K^+$ channel listed in Table 8.1.

LGICs include nicotinic acetylcholine receptors, γ-aminobutyric acid (GABA) receptors, glycine receptors and serotonin (5-hydroxytryptamine) 5-$HT_3$ receptors. They are typically pentamers, with each subunit comprising four transmembrane helices clustering around a central channel or pore. Each peptide subunit is orientated so that hydrophilic chains face towards the channel and hydrophobic chains towards the membrane lipid bilayer. Binding of an active ligand to the receptor causes a conformational change in the protein and results in extremely fast opening of the ion channel. The nicotinic acetylcholine receptor is a good example of this type of structure (Fig. 1.1). It requires the binding of two molecules of acetylcholine for channel opening, which lasts only milliseconds because the ligand rapidly dissociates and is inactivated. Drugs may modulate LGIC activity by binding directly to the channel, or indirectly by acting on G-protein-coupled receptors (GPCRs; discussed later), with the subsequent intracellular events then affecting the status of the LGIC.

VGICs include $Ca^{2+}$, $Na^+$ and $K^+$ channels. The $K^+$ channels consist of four distinct peptide subunits, each of which has between two and six transmembrane helices; in $Ca^{2+}$ and $Na^+$ channels there are four domains, each with six transmembrane helices, within a single large protein. The pore-forming regions of the transmembrane helices are largely responsible for the selectivity of the channel for a particular ion. Both $Na^+$ and $K^+$ channels are inactivated after opening; this is produced by an intracellular loop of the channel, which blocks the open channel from the intracellular end. The activity of VGICs may thus be modulated by drugs acting directly on the channel, such as local anaesthetics which maintain $Na^+$ channels in the inactivated site by binding at an intracellular site (Chapter 18). Drugs may also modulate

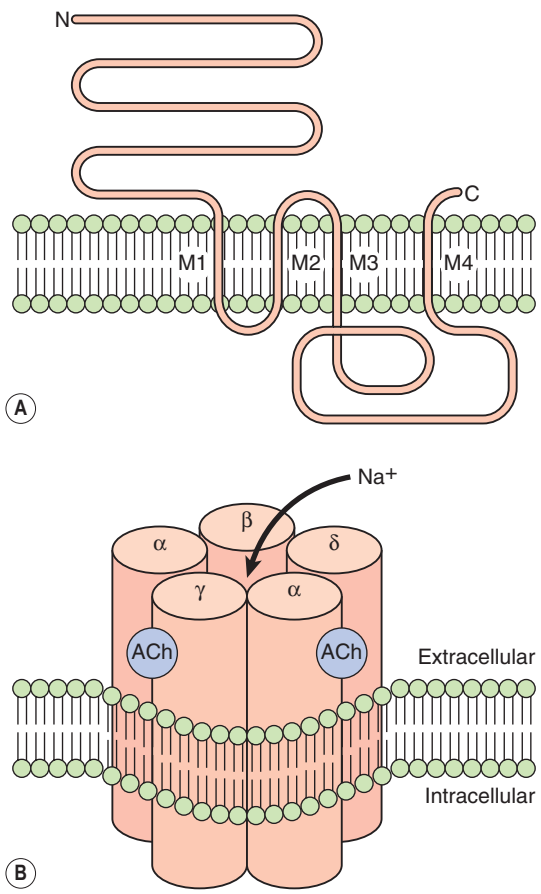


***Fig. 1.1*** **The acetylcholine nicotinic receptor, a typical ligand-gated transmembrane ion channel.** (A) The receptor is constructed from subunits with four transmembrane regions (M1–M4). (B) Five subunits are assembled into the ion channel, which has two sites for acetylcholine binding, each formed by the extracellular domains of two adjacent subunits. On acetylcholine binding, the central pore undergoes conformational change that allows selective $Na^+$ ion flow down its concentration gradient into the cell. *N*, amino terminus; *C*, carboxyl terminus.

VGICs indirectly via intracellular signals from other receptors. For example, L-type $Ca^{2+}$ channels are inactivated directly by calcium channel blockers, but also indirectly by drugs which reduce intracellular signalling from the $\beta_1$ subtype of adrenoceptors (see Fig. 5.5).

The ability of highly variable transmembrane subunits to assemble in a number of configurations leads to the existence of many different subtypes of channels for a single ion. For example, there are many different voltage-gated $Ca^{2+}$ channels (L, N, P/Q, R and T types).

## Seven-transmembrane receptors

Also known as 7TM receptors, heptahelical receptors and serpentine receptors, this family is an extremely important group, as the human genome has about 750 sequences for

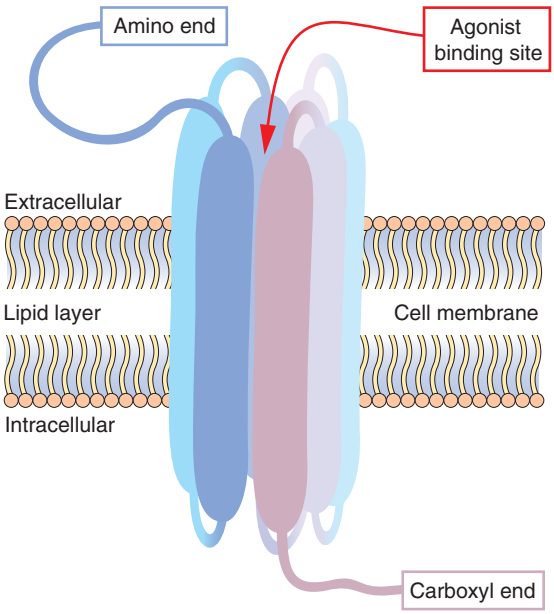


***Fig. 1.2*** **Hypothetical seven-transmembrane (7TM) receptor.** The 7TM receptor is a single polypeptide chain with its amino (N-) terminus outside the cell membrane and its carboxyl (C-) terminus inside the cell. The chain is folded such that it crosses the membrane seven times, with each hydrophobic transmembrane region shown here as a thickened segment. The hydrophilic extracellular loops create a confined three-dimensional environment in which only the appropriate ligand can bind. Other potential ligands may be too large for the site or show much weaker binding characteristics. Selective ligand binding causes conformational change in the three-dimensional form of the receptor, which activates signalling proteins and enzymes associated with the intracellular loops, such as G-proteins and nucleotide cyclases.

7TM receptors and they are the targets of over 30% of current drugs. The function of over a hundred 7TM receptors is still unknown. The structure of a hypothetical 7TM receptor is shown in Fig. 1.2; the N-terminal region of the polypeptide chain is on the extracellular side of the membrane, and the polypeptide traverses the membrane seven times with helical regions, so that the C terminus is on the inside of the cell. The extracellular loops provide the receptor site for an appropriate agonist (a natural ligand or a drug), the binding of which alters the three-dimensional conformation of the receptor protein. The intracellular loops are involved in coupling this conformational change to the second messenger system, usually via a heterotrimeric G-protein, giving rise to the term GPCR.

### The G-protein system

The heterotrimeric G-protein system (Fig. 1.3) consists of α, β and γ subunits.

- **The α-subunit.** More than 20 different types have been identified, belonging to four families ($\alpha_s$, $\alpha_i$, $\alpha_q$ and $\alpha_{12/13}$). The α-subunit is important because it binds guanosine

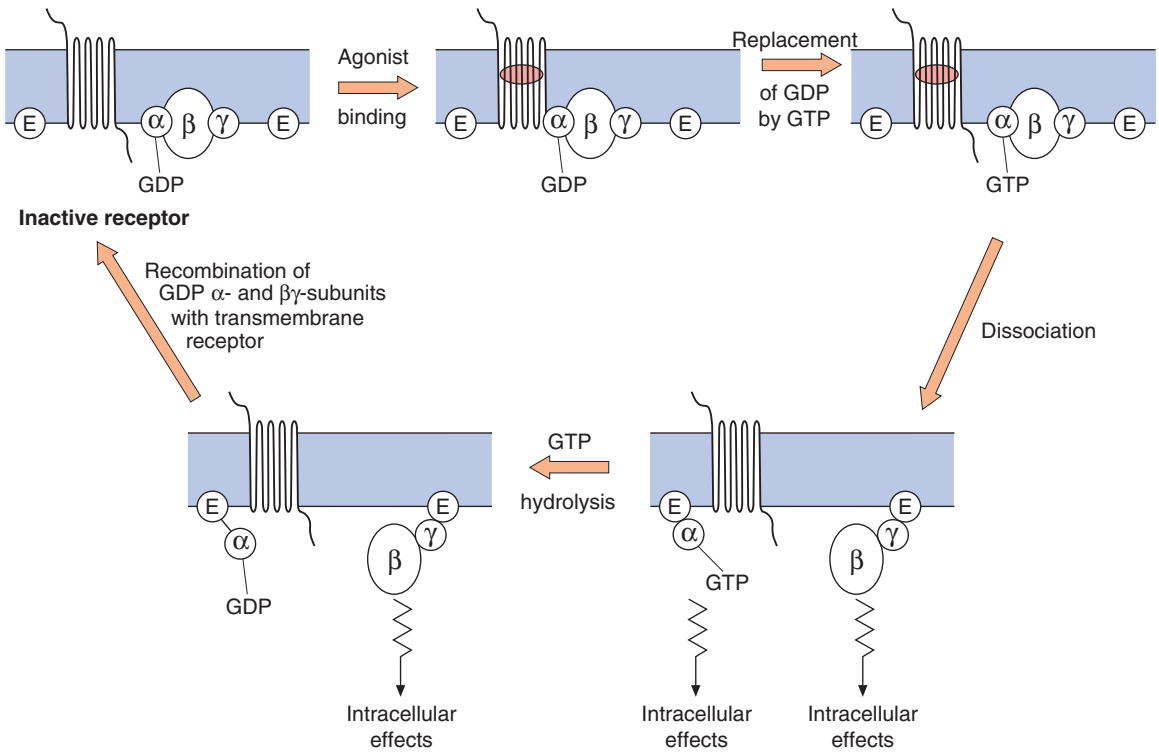


***Fig. 1.3*** **The functioning of G-protein subunits.** Ligand (agonist) binding results in replacement of GDP on the α-subunit by guanosine triphosphate (GTP) and the dissociation of the α- and βγ-subunits, each of which can affect a range of intracellular systems (shown as E in the figure) such as second messengers (e.g. adenylyl cyclase and phospholipase C), or other enzymes and ion channels (see Figs 1.4 and 1.5). Hydrolysis of GTP to GDP inactivates the α-subunit, which then recombines with the βγ-dimer to reform the inactive receptor.

diphosphate (GDP) and guanosine triphosphate (GTP) in its inactive and active states, respectively; it also has GTPase activity, which is involved in terminating its own activity. When an agonist binds to the receptor, GDP (which is normally present on the α-subunit) is replaced by GTP. The active α-subunit–GTP dissociates from the βγ-subunits and can activate enzymes such as adenylyl cyclase. The α-subunit–GTP complex is inactivated when the GTP is hydrolysed back to GDP by the GTPase.

- **The βγ-complex.** There are many different isoforms of β- and γ-subunits that can combine into dimers, the normal function of which is to inhibit the α-subunit when the receptor is unoccupied. When the receptor is occupied by a ligand, the βγ-complex dissociates from the α-subunit and can itself activate cellular enzymes, such as phospholipase C. The α-subunit–GDP and βγ-subunit then recombine with the receptor protein to give the inactive form of the receptor–G-protein complex.

## *Second messenger systems*

Second messengers are the key distributors of an external signal, as they are released into the cytosol as a consequence of receptor activation and are responsible for affecting a wide variety of intracellular enzymes, ion channels and transporters. There are two complementary second messenger systems: the cyclic nucleotide system and the phosphatidylinositol system (Fig. 1.4).

### Cyclic nucleotide system

This system is based on cyclic nucleotides, such as:

- Cyclic adenosine monophosphate (cAMP), which is synthesised from adenosine triphosphate (ATP) by adenylyl cyclase. cAMP induces numerous cellular responses by activating protein kinase A (PKA), which phosphorylates proteins, many of which are enzymes. Phosphorylation can either activate or suppress cell activity.
- Cyclic guanosine monophosphate (cGMP), which is synthesised from GTP by guanylyl cyclase. cGMP exerts most of its actions through protein kinase G, which, when activated by cGMP, phosphorylates target proteins.

There are 10 isoforms of adenylyl cyclase; these show different tissue distributions and could be important sites of selective drug action in the future. The cyclic nucleotide second messenger (cAMP or cGMP) is inactivated by hydrolysis by phosphodiesterase (PDE) isoenzymes to give AMP or GMP. There are 11 different families of PDE isoenzymes (Table 1.1), some of which are the targets of important drug groups, including selective PDE4 inhibitors used in respiratory disease and PDE5 inhibitors used in erectile dysfunction.

### The phosphatidylinositol system

The other second messenger system is based on inositol 1,4,5-triphosphate ($IP_3$) and diacylglycerol (DAG),

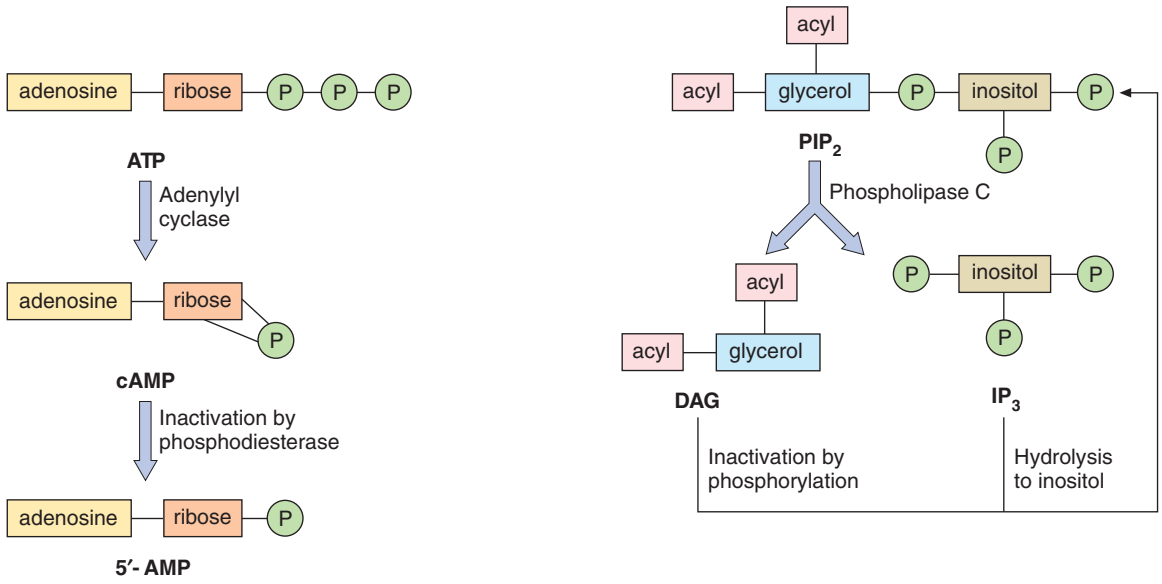


***Fig. 1.4*** **Second messenger systems.** Stimulation of G-protein-coupled receptors produces intracellular changes by activating or inhibiting cascades of second messengers. Examples are cyclic adenosine monophosphate (cAMP), and diacylglycerol (DAG) and inositol triphosphate ($IP_3$) formed from phosphatidylinositol 4,5-bisphosphate ($PIP_2$). See also Fig. 1.5.

which are synthesised from the membrane phospholipid phosphatidylinositol 4,5-bisphosphate ($PIP_2$) by phospholipase C (see Fig. 1.4). There are a number of isoenzymes of phospholipase C, which may be activated by the α-subunit–GTP or βγ-subunits of G-proteins. The main function of $IP_3$ is to mobilise $Ca^{2+}$ in cells. With the increase in $Ca^{2+}$ brought about by $IP_3$, DAG is able to activate protein kinase C (PKC) and phosphorylate target proteins. $IP_3$ and DAG are then inactivated and converted back to $PIP_2$.

Which second messenger system is activated when a GPCR binds a selective ligand depends primarily on the nature of the Gα-subunit, as illustrated in Fig. 1.5:

- $G_s$: Stimulation of adenylyl cyclase (increases cAMP), activation of $Ca^{2+}$ channels
- $G_{i/o}$: Inhibition of adenylyl cyclase (reduces cAMP), inhibition of $Ca^{2+}$ channels, activation of $K^+$ channels
- $G_{q/11}$: Activation of phospholipase C, leading to DAG and $IP_3$ signalling
- $G_{12/13}$: Activation of cytoskeletal and other proteins via the Rho family of GTPases, which influence smooth muscle contraction and proliferation

The βγ-complex also has signalling activity: it can activate phospholipases and modulate some types of $K^+$ and $Ca^{2+}$ channels.

Activation of these second messenger systems by G-protein subunits thus affects many cellular processes such as enzyme activity (either directly or by altering gene transcription), contractile proteins, ion channels (affecting depolarisation of the cell) and cytokine production. The many different isoforms of $G_\alpha$, $G_\beta$ and $G_\gamma$ proteins may represent important future targets for selective drugs.

It is increasingly recognised that GPCRs may assemble into dimers of identical 7TM proteins (homodimers) or into heterodimers of different receptor proteins; the functional consequences of GPCR dimerisation and its implications for drug therapy are unclear.

### *Protease-activated receptors*

Protease-activated receptors (PARs) are GPCRs stimulated unusually by a 'tethered ligand' located within the N terminus of the receptor itself, rather than by an independent ligand. Proteolysis of the N-terminal sequence by serine proteases such as thrombin, trypsin and tryptase enables the residual tethered ligand to bind to the receptor within the second extracellular loop (Fig. 1.6). To date, four protease-activated receptors (PAR 1–4) have been identified, each with distinct N-terminal cleavage sites and different tethered ligands. The receptors appear to play roles in platelet activation and clotting (Chapter 11), and in inflammation and tissue repair. Most of the actions of PAR are mediated by $G_i$, $G_q$ and $G_{12/13}$.

## Enzyme-linked transmembrane receptors

Enzyme-linked receptors, most notably the receptor tyrosine kinases, are similar to the GPCRs in that they have a ligand-binding domain on the surface of the cell membrane; they traverse the membrane; and they have an intracellular effector region (Fig. 1.7). They differ from GPCRs in their extracellular ligand-binding domain, which is very large to accommodate their polypeptide ligands (including hormones, growth factors and cytokines), and in having only one transmembrane helical region. Importantly, their intracellular action requires a linked enzymic domain, most commonly an integral kinase which activates the receptor itself or other proteins by phosphorylation. Activation of enzyme-linked receptors enables binding and activation of many intracellular signalling proteins, leading to changes

**Table 1.1 Isoenzymes of phosphodiesterase**

| Enzyme | Main substrate | Main site(s) | Examples of inhibitors | Therapeutic potential |
|---|---|---|---|---|
| PDE1 | cAMP + cGMP | Heart, brain, lung, lymphocytes, vascular smooth muscle | – | Atherosclerosis? |
| PDE2 | cAMP + cGMP | Adrenal gland, brain, heart, lung, liver, platelets, endothelial cells | – | Involved in memory? |
| PDE3 | cAMP + cGMP | Heart, lung, liver, platelets, adipose tissue, inflammatory cells, smooth muscle | Aminophylline<br>Enoximone<br>Milrinone<br>Cilostazol | Asthma (Chapter 12)<br>Congestive heart failure (Chapter 7)<br>Peripheral vascular disease (Chapter 10) |
| PDE4 | cAMP | Sertoli cells, endothelial cells, kidney, brain, heart, liver, lung, inflammatory cells | Aminophylline<br>Roflumilast | Asthma, COPD (Chapter 12)<br>Inflammation<br>IBD? |
| PDE5 | cGMP | Smooth muscle, endothelium, neurons, lung, platelets | Sildenafil<br>Tadalafil<br>Vardenafil<br>Dipyridamole | Erectile dysfunction (Chapter 16)<br>Pulmonary hypertension (Chapter 6) |
| PDE6 | cGMP | Photoreceptors, pineal gland | Dipyridamole<br>Sildenafil (weak) | Undefined |
| PDE7 | cAMP | Skeletal muscle, heart, kidney, brain, pancreas, spinal cord, T-lymphocytes | – | Inflammation (combined with PDE4 inhibitor)?<br>Spinal cord injury? |
| PDE8 | cAMP | Testes, eye, liver, skeletal muscle, heart, kidney, ovary, brain, T-lymphocytes | – | Undefined |
| PDE9 | cGMP | Kidney, liver, lung, brain | – | Undefined |
| PDE10 | cAMP + cGMP | Testes, brain, thyroid | – | Schizophrenia? |
| PDE11 | cAMP + cGMP | Skeletal muscle, prostate, kidney, liver, pituitary and salivary glands, testes | Tadalafil (weak) | Undefined |

*cAMP*, Cyclic adenosine monophosphate; *cGMP*, cyclic guanosine monophosphate; *COPD*, chronic obstructive pulmonary disease; *IBD*, inflammatory bowel disease, *PDE*, phosphodiesterase.

in gene transcription and in many cellular functions. There are five families of enzyme-linked transmembrane receptors:

- **Receptor tyrosine kinase (RTK) family.** Ligand binding causes receptor dimerisation and transphosphorylation of tyrosine residues within the receptor itself and sometimes in associated cytoplasmic proteins. Up to 20 classes of RTK include receptors for growth factors, many of which signal via proteins of the mitogen-activated protein (MAP) kinase cascade, leading to effects on gene transcription, apoptosis and cell division. Constitutive overactivity of an RTK called Bcr-Abl causes leucocyte proliferation in chronic myeloid leukaemia, which is treated with imatinib, a drug that blocks the uncontrolled RTK activity. Several other RTKs are also the targets of anticancer drugs.
- **Tyrosine phosphatase receptor family.** These dephosphorylate tyrosines on other transmembrane receptors or cytoplasmic proteins; they are particularly common in immune cells.
- **Tyrosine kinase-associated receptor family (or nonreceptor tyrosine kinases).** These lack integral kinase activity but activate separate kinases associated with the receptor; examples include inflammatory cytokine receptors and signalling via the JAK/Stat pathways to affect inflammatory gene expression.
- **Receptor serine-threonine kinase family.** Activation of these phosphorylates serine and threonine residues in target cytosolic proteins; everolimus is a serine-threonine kinase inhibitor used in renal and pancreatic cancer.
- **Receptor guanylyl cyclase family.** Members of this family catalyse the formation of cGMP from GTP via a cytosolic domain.

## Intracellular (nuclear) receptors

Many hormones act at intracellular receptors to produce long-term changes in cellular activity by altering the genetic expression of enzymes, cytokines or receptor proteins. Such hormones are lipophilic to facilitate their movement across the cell membrane. Examples include the thyroid hormones and the large group of steroid hormones, including glucocorticoids, mineralocorticoids and the sex steroid hormones. Their actions on DNA transcription are mediated by interactions with intracellular receptors (Table 1.2) located either in the cytoplasm (type 1) or the nucleus (type 2).

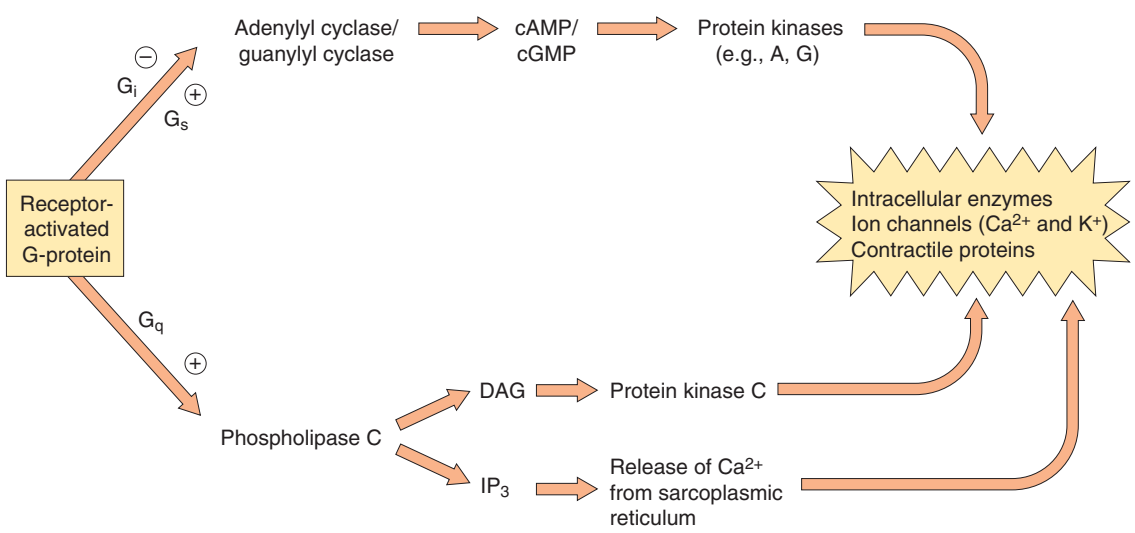


***Fig. 1.5*** **The intracellular consequences of receptor activation.** The second messengers cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), diacylglycerol (DAG) and inositol 1,4,5-triphosphate ($IP_3$) produce a number of intracellular changes, either directly or indirectly via actions on protein kinases (which phosphorylate other proteins) or by actions on ion channels. The pathways can be activated or inhibited depending upon the type of receptor and G-protein and the particular ligand stimulating the receptor. The effect of the same second messenger can vary depending upon the biochemical functioning of cells in different tissues.

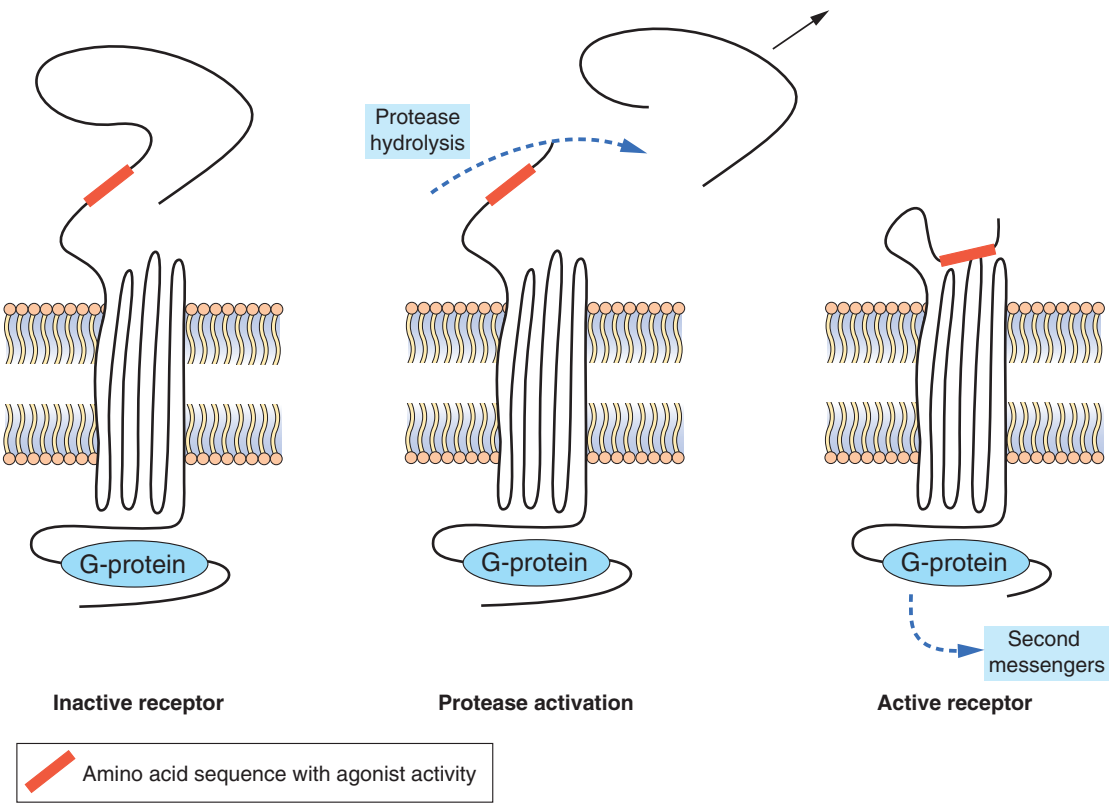


***Fig. 1.6*** **Protease-activated receptors.** These G-protein-coupled receptors are activated by proteases such as thrombin which hydrolyse the extracellular peptide chain to expose a segment that acts as a tethered ligand (shown in red) and activates the receptor. The receptor is inactivated by phosphorylation of the intracellular (C-terminal) part of the receptor protein.

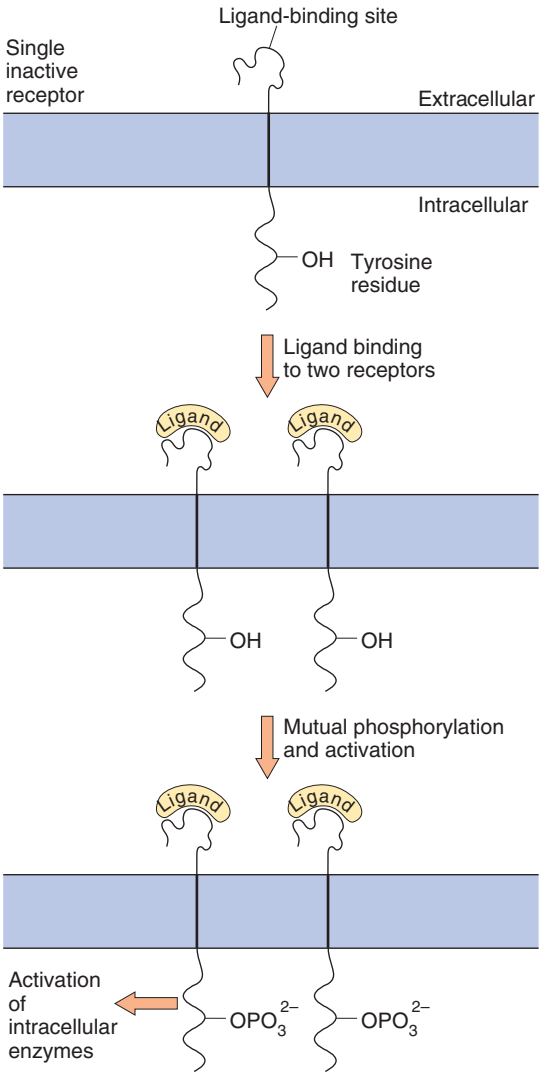


***Fig. 1.7*** **Enzyme-linked transmembrane receptors.** This receptor tyrosine kinase has a large extracellular domain, a single transmembrane segment and an integral kinase domain. Ligand binding causes phosphorylation of tyrosine residues on the receptor and on other target proteins, leading to intracellular changes in cell behaviour. Other enzyme-linked receptors have tyrosine phosphatase, serine-threonine kinase or guanylyl cyclase enzymic activity.

**Table 1.2 Some families of intracellular receptors**

| | Subtypes |
|---|---|
| **Type 1 (cytoplasmic)** | |
| Oestrogen receptors | ER (α, β) |
| Progesterone receptors | PR (A, B) |
| Androgen receptors | AR (A, B) |
| Glucocorticoid receptor | GR |
| Mineralocorticoid receptor | MR |
| **Type 2 (nuclear)** | |
| Thyroid hormone receptors | TR ($\alpha_1$, $\beta_1$, $\beta_2$) |
| Vitamin D receptor | VDR |
| Retinoic acid receptors | RAR (α, β, γ) |
| Retinoid X receptors | RXR (α, β, γ) |
| Liver X (oxysterol) receptors | LXR (α, β) |
| Peroxisome proliferator-activated receptors | PPAR (α, β/δ, γ) |

**Table 1.3 The structure of steroid hormone receptors**

| Section of protein | Domain | Role |
|---|---|---|
| A/B | N-terminal variable domain | Regulates transcriptional activity |
| C | DNA-binding domain (DBD) | Highly conserved; binds receptor to hormone response element in DNA by two zinc-containing regions |
| D | Hinge region | Enables intracellular translocation to the nucleus |
| E | Ligand-binding domain (LBD) | Moderately conserved; enables specific ligand binding; contains nuclear localisation sequence (NLS); also binds chaperone proteins and facilitates receptor dimerisation |
| F | C-terminal domain | Highly variable; unknown function |

The intracellular receptor typically includes a highly conserved DNA-binding domain with zinc-containing loops and a variable ligand-binding domain (Table 1.3). The sequence of hormone binding and action for type 1 intracellular receptors is shown in Fig. 1.8. Type 1 receptors are typically found in an inactive form in the cytoplasm linked to chaperone proteins such as heat-shock proteins (HSPs). Binding of the hormone induces conformational change in the receptor; this causes dissociation of the HSP and reveals a nuclear localisation sequence (or NLS) which enables the hormone–receptor complex to pass through nuclear membrane pores into the nucleus. Via their DNA-binding domain, the active hormone–receptor complexes can interact with hormone response elements (HRE) at numerous sites in the genome. Binding to the HRE usually activates gene transcription, but sometimes it silences gene expression and decreases mRNA synthesis.

Translocation and binding to DNA involves a variety of different chaperone, co-activator and co-repressor proteins, and the system is considerably more complex than indicated

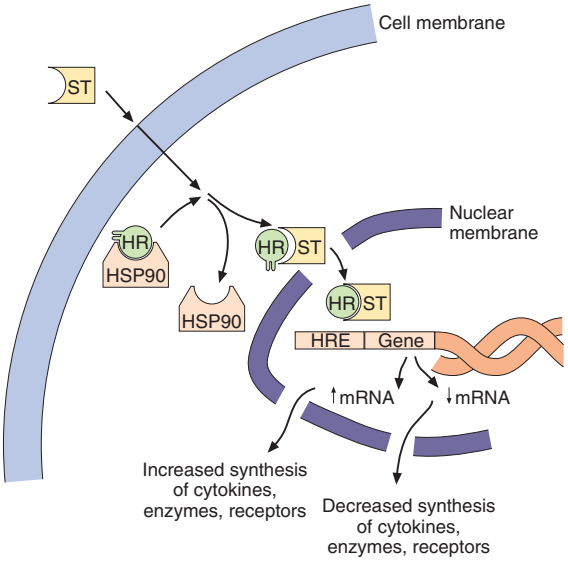


***Fig. 1.8*** **The activation of intracellular hormone receptors.** Steroid hormones (ST) are lipid-soluble compounds which readily cross cell membranes and bind to their intracellular receptors (HR). This binding displaces a chaperone protein called heat-shock protein (HSP90) and the hormone–receptor complex enters the nucleus, where it can increase or decrease gene expression by binding to hormone response elements (HRE) on DNA. Intracellular receptors for many other ligands are activated in the nucleus itself.

in Fig. 1.8. Co-activators are transcriptional cofactors that also bind to the receptor and increase the level of gene induction; an example is histone acetylase, which facilitates transcription by increasing the ease of unravelling of DNA from histone proteins. Co-repressors also bind to the receptor and repress gene activation; an example is histone deacetylase, which prevents further transcription by tightening histone interaction with the DNA.

Type 2 intracellular receptors, such as the thyroid hormone receptors (TR) and the peroxisome proliferator-activated receptor (PPAR) family (see Table 1.2), are found within the nucleus bound to co-repressor proteins, which are liberated by ligand binding without a receptor translocation step from the cytoplasm. PPAR nuclear receptors function as sensors for endogenous fatty acids, including eicosanoids (Chapter 29), and regulate the expression of genes that influence metabolic events.

Intracellular receptors are the molecular targets of 10–15% of marketed drugs, including steroid drugs acting at type 1 receptors and other drugs acting at type 2 receptors. Steroids show selectivity for different type 1 intracellular receptors (ER, PR, AR, GR, MR; see Table 1.2), which determine the spectrum of gene expression that is affected (Chapters 14, 44, 45 and 46). Steroid effects are also determined by the differential expression of these receptors in different tissues. Intracellular hormone–receptor complexes typically dimerise to bind to their HRE sites on DNA. Steroid receptors form homodimers (e.g. ER–ER), while most type 2 receptors form heterodimers, usually with RXR (e.g. RAR–RXR). The thiazolidinedione drugs used in diabetes mellitus and the fibrate class of lipid-lowering drugs act on specific members of the PPAR family of type 2 receptors.

## OTHER SITES OF DRUG ACTION

Probably every protein in the human body has the potential to have its structure or activity altered by foreign compounds. Traditionally, all drug targets were described pharmacologically as ‘receptors’, although many drug targets would not be defined as receptors in biochemical terms; in addition to the receptor types discussed previously, drugs may act at numerous other sites.

- **Cell-membrane ion pumps.** In contrast to passive diffusion, primary active transport of ions against their concentration gradients occurs via ATP-dependent ion pumps, which may be drug targets. For example, $Na^+/K^+$-ATPase in the brain is activated by the anticonvulsant drug phenytoin, whereas in cardiac tissue it is inhibited by digoxin; $K^+/H^+$-ATPase in gastric parietal cells is inhibited by proton pump inhibitors such as omeprazole.
- **Transporter (carrier) proteins.** Secondary active transport involves carrier proteins, which transport a specific ion or organic molecule across a membrane; the energy for the transport derives not from a coupled ATPase but from the co-transport of another molecule down its concentration gradient, either in the same direction (symport) or in the opposite direction (antiport). Examples include:
  - $Na^+/Cl^-$ co-transport in the renal tubule, which is blocked by thiazide diuretics (Chapter 14);
  - the reuptake of neurotransmitters into nerve terminals by a number of transporters selectively blocked by classes of antidepressant drugs (Chapter 22).
- **Enzymes.** Many drugs act on the intracellular or extracellular enzymes that synthesise or degrade the endogenous ligands for extracellular or intracellular receptors, or which are required for growth of bacterial, viral or tumour cells. Table 1.4 provides examples of drug groups that act on enzyme targets. The PDE isoenzymes that regulate second messenger molecules are important drug targets and are listed in Table 1.1. In addition to being sites of drug action, enzymes are involved in inactivating many drugs, while some drugs are administered as inactive precursors (pro-drugs) that are enzymatically activated (Chapter 2).
- **Adhesion molecules**. These regulate the cell-surface interactions of immune cells with endothelial and other cells. Natalizumab is a monoclonal antibody directed against the $\alpha_4$-integrin component of vascular cell adhesion molecule (VCAM)-1 and is used to inhibit the autoimmune activity of lymphocytes in acute relapsing multiple sclerosis. Other monoclonal antibody-based therapies are targeted at cellular and humoral proteins, including cytokines and intracellular signalling proteins to suppress inflammatory cell proliferation, activity and recruitment in immune disease.
- **Organelles and structural proteins.** Examples include some antimicrobials that interfere with the functioning of ribosomal proteins in bacteria, and some types of anticancer drugs that interrupt mitotic cell division by blocking microtubule formation.

The sites of action of some drugs remain unknown or poorly understood. Conversely, many receptors have

**Table 1.4 Examples of enzymes as drug targets**

| Enzyme | Drug class or use | Examples |
|---|---|---|
| Acetylcholinesterase (AChE) | AChE inhibitors (Chapter 27) | Neostigmine, edrophonium, organophosphates |
| Angiotensin-converting enzyme (ACE) | ACE inhibitors (Chapter 6) | Captopril, perindopril, ramipril |
| Antithrombin (AT)III | Heparin anticoagulants (*enhancers* of antithrombin III) (Chapter 10) | Enoxaparin, dalteparin |
| Carbonic anhydrase | Carbonic anhydrase inhibitors (Chapters 14, 50) | Acetazolamide |
| Cyclo-oxygenase (COX)-1 | Nonsteroidal anti-inflammatory drugs (NSAIDs) (Chapter 29) | Ibuprofen, indometacin, naproxen |
| Cyclo-oxygenase (COX)-2 | Selective COX-2 inhibitors (Chapter 29) | Celecoxib, etoricoxib |
| Dihydrofolate reductase | Folate antagonists (Chapters 51, 52) | Trimethoprim, methotrexate |
| DOPA decarboxylase | Peripheral decarboxylase inhibitors (PDIs) (Chapter 24) | Carbidopa, benserazide |
| Coagulation factor Xa | Direct inhibitors of Factor Xa (Chapter 11) | Rivaroxaban |
| HMG-CoA reductase | Statins (HMG-CoA reductase inhibitors) (Chapter 48) | Atorvastatin, simvastatin |
| Monoamine oxidases (MAOs) A and B | MAO-A and MAO-B inhibitors (Chapters 22, 24) | Moclobemide, selegiline |
| Phosphodiesterase (PDE) isoenzymes | PDE inhibitors (Chapters 12, 16) | Theophylline, sildenafil (see Table 1.1) |
| Reverse transcriptase (RT) | Nucleos(t)ide and nonnucleoside RT inhibitors (Chapter 51) | Zidovudine, efavirenz |
| Ribonucleotide reductase | Ribonucleotide reductase inhibitor (Chapter 52) | Hydroxycarbamide (hydroxyurea) |
| Thrombin | Direct thrombin inhibitors (Chapter 11) | Dabigatran |
| Viral proteases | HIV/hepatitis protease inhibitors (Chapter 51) | Saquinavir, boceprevir |
| Vitamin K epoxide reductase | Coumarin anticoagulants (Chapter 11) | Warfarin |
| Xanthine oxidase | Xanthine oxidase inhibitors (Chapter 31) | Allopurinol |

been discovered for which the natural ligands are not yet recognised; these orphan receptors may represent targets for novel drugs when their pharmacology is better understood.

## PROPERTIES OF RECEPTORS

### Receptor binding

The binding of endogenous ligands and most drugs to their receptors is normally reversible; consequently, the intensity and duration of the intracellular changes are dependent on repeated ligand–receptor interactions that continue for as long as the ligand molecules remain in the local environment of the receptors. The duration of activity of a reversible drug therefore depends mainly on its distribution and elimination from the body (pharmacokinetics), which typically requires hours or days (Chapter 2), not on the duration of binding of a drug molecule to its receptor, which may last only a fraction of a second. For a reversible drug, the extent of drug binding to the receptor (receptor occupancy) is proportional to the drug concentration; the higher the concentration, the greater the occupancy. The interaction between a reversible ligand and its receptor does not involve covalent chemical bonds but weaker, reversible forces, such as:

- ionic bonding between ionisable groups in the ligand (e.g. $NH_3^+$) and the receptor (e.g. $COO^-$);
- hydrogen bonding between amino-, hydroxyl-, keto- and other groups in the ligand and the receptor;
- hydrophobic interactions between lipid-soluble sites in the ligand and receptor;
- van der Waals forces, which are very weak interatomic attractions.

The receptor protein is not a rigid structure: binding of the ligand alters the conformation and biological properties of the protein, enabling it to trigger intracellular signalling pathways. There is growing recognition that different ligands may stabilise different conformational states of the same receptor that are distinct from those produced by the endogenous ligand. Rather than simply switching a receptor between inactive and active states, a 'biased' ligand may produce preferential receptor signalling via specific G-protein pathways or by non-G-protein effectors, such as the family of arrestin proteins, leading to different cellular behaviours. Drugs may therefore be developed with functional selectivity

to generate different cell responses from the same receptor, in contrast to the classical concept of different responses being generated by drugs acting at different receptors.

## Receptor selectivity

There are numerous possible extracellular and intracellular signals produced in the body, which can affect many different processes. Therefore a fundamental property of a useful ligand–receptor interaction is its *selectivity*; that is, the extent to which the receptor can recognise and respond to the correct signals, represented by one ligand or group of related ligands. Some receptors show high selectivity and bind a single endogenous ligand (e.g. acetylcholine is the only endogenous ligand that binds to $N_1$ nicotinic receptors; see Chapter 4), whereas other receptors are less selective and will bind a number of related endogenous ligands (e.g. the $\beta_1$-adrenoceptors on the heart will bind noradrenaline, adrenaline and to some extent dopamine, all of which are catecholamines).

The ability of receptors to recognise and bind the appropriate ligand depends on the intrinsic characteristics of the chemical structure of the ligand. The formulae of a few ligand families that bind to different receptors are shown in Fig. 1.9; differences in structure that determine selectivity of action between receptors may be subtle, such as the those illustrated between the structures of testosterone and progesterone, which nevertheless have markedly different hormonal effects on the body due to their receptor selectivity. Receptors are protein chains folded into tertiary and quaternary structures such that the necessary arrangement of specific binding centres is brought together in a small volume – the receptor site (Fig. 1.10). Receptor selectivity occurs because the three-dimensional organisation of the different sites for reversible binding (such as anion and cation sites, lipid centres and hydrogen-bonding sites) corresponds better to the three-dimensional structure of the endogenous ligand than to that of other ligands.

There may be a number of subtypes of a receptor, all of which can bind the same common ligand but which differ in their ability to recognise particular variants or derivatives of that ligand. The different characteristics of the receptor subtypes therefore allow a drug (or natural ligand) with a particular three-dimensional structure to show selective actions by recognising one receptor preferentially, with fewer unwanted effects from the stimulation or blockade of related receptors. For example, $\alpha_1$-, $\alpha_2$-, $\beta_1$-, $\beta_2$- and $\beta_3$-adrenoceptors all bind adrenaline, but isoprenaline, a synthetic derivative of adrenaline, binds selectively to the three β-adrenoceptor subtypes rather than the two α-adrenoceptor subtypes (Chapter 4). As the adrenoceptor subtypes occur to a different extent in different tissues, and produce different intracellular changes when stimulated or blocked, drugs can be designed that have highly selective and localised actions. The cardioselective β-adrenoceptor antagonists such as bisoprolol are selective blockers of the $\beta_1$-adrenoceptor subtype that predominates on cardiac smooth muscle, with much less binding to the $\beta_2$-adrenoceptors that predominate on bronchial smooth muscle. Although ligands may have a much higher affinity for one receptor subtype over another, this is never absolute, so the term *selective* is preferred over *specific*.

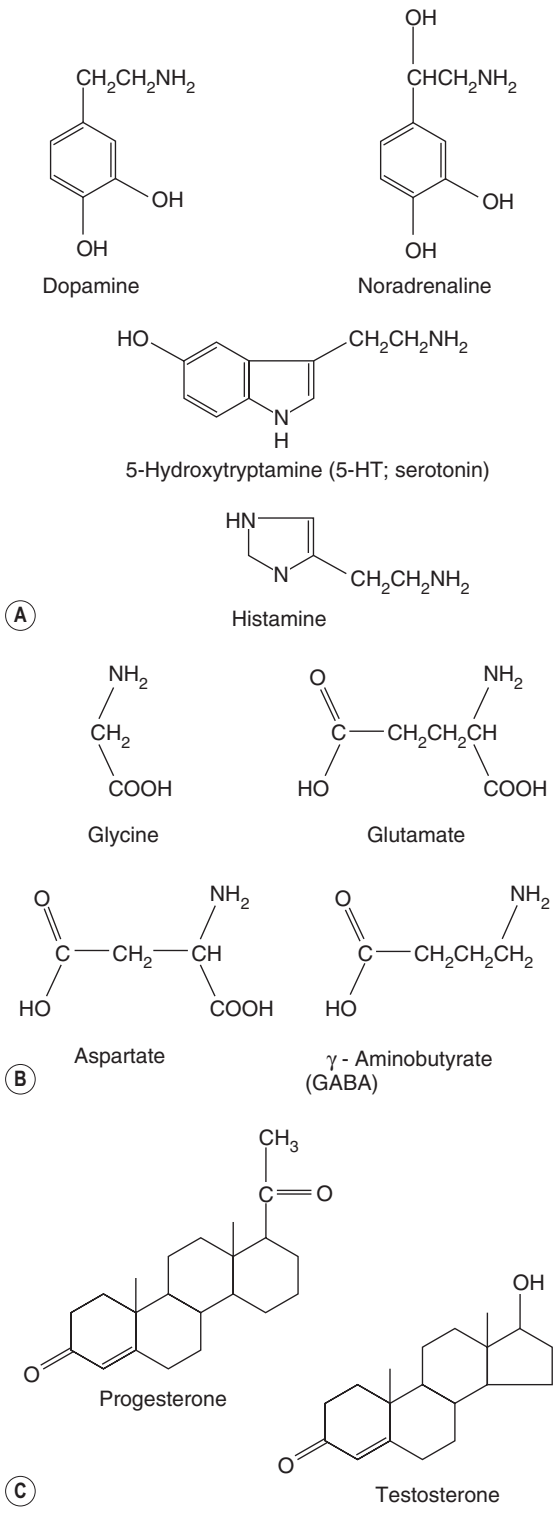


***Fig. 1.9*** **Groups of related chemicals that show selectivity for different receptor subtypes in spite of similar structure.** (A) Biogenic amines; (B) amino acids; (C) steroids.

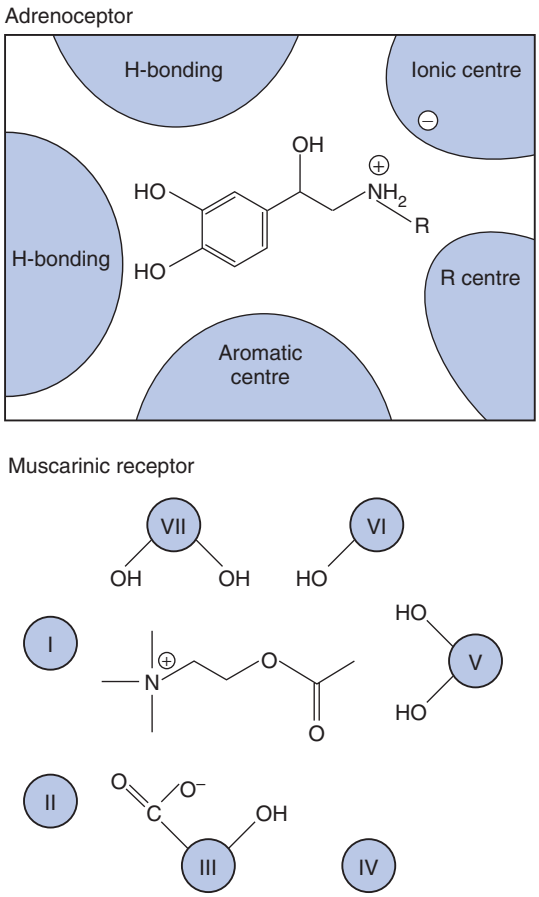


***Fig. 1.10*** **Receptor ligand-binding sites.** The coloured areas are schematic representations of the regions of the adrenoceptor (top) and muscarinic receptor (bottom) responsible for binding their respective catecholamine and acetylcholine ligands. In the muscarinic receptor, cross-sections of the seven transmembrane segments are labelled I–VII. Different segments provide different properties (hydrogen bonding, anionic site, etc.) to make up the active binding site.

Traditionally, receptor subtypes were discovered pharmacologically when a new agonist or antagonist compound was found to alter some but not all of the activities of a currently known receptor class. Developments in molecular biology, including the Human Genome Project, have accelerated the recognition and cloning of new receptors and receptor subtypes, including orphan receptors for which the natural ligands are unknown. These developments are important in guiding development of new drugs with greater selectivity and fewer unwanted effects. Based on such information it is recognised that there are multiple types of most receptors, and that there is genetic variation among individuals in the structures, properties and abundance of these receptors, which can lead to differences in drug responses (pharmacogenetic variation; discussed later). Greater understanding of genetic differences underlying human variability in drug responses offers the potential for individualisation of the mode of treatment and selection of the optimal drug and dosage (personalised medicine).

## Drug stereochemistry and activity

The three-dimensional spatial organisation of receptors means that the ligand must have the correct configuration to fit the receptor, analogous to fitting a right hand into a right-handed glove. Drugs and other organic molecules show stereoisomerism if they contain four different chemical groups attached to a single carbon atom, or one or more double bonds, with the result that compounds with the same molecular formula can exist in different three-dimensional configurations. If a drug is an equal (racemic) mixture of two stereoisomers, the stereoisomers may show different receptor binding characteristics and biological properties. Most often, one stereoisomer is pharmacologically active while the other is inactive, but in some cases the inactive isomer may be responsible for the unwanted effects of the racemic mixture. Alternatively the two isomers may be active at different receptor subtypes and have synergistic or even opposing actions. The different isomers may also show different rates of metabolism. As a consequence, there has been a trend for the development of single stereoisomers of drugs for therapeutic use; one of the earliest examples was the use of levodopa, the levo-isomer of dihydroxyphenylalanine (DOPA) in Parkinson's disease (Chapter 24).

## Receptor numbers

The number of receptors present in, or on the surface of, a cell is not static. There is usually a high turnover of receptors being formed and removed continuously. Cell-membrane receptor proteins are synthesised in the endoplasmic reticulum and transported to the plasma membrane. Regulation of functional receptor numbers in the membrane occurs both by transport to the membrane (often as homo- or heterodimers) and by removal by internalisation. The number of receptors within the cell membrane may be altered by the drug being used for treatment, with either an increase in receptor number (*upregulation*) or a decrease (*downregulation*) and a consequent change in the ability of the drug to effect the desired therapeutic response. This change may be an unwanted loss of drug activity contributing to tolerance to the effects of the drug (e.g. opioids; Chapter 19). As a result, increased doses may be needed to maintain the same activity. Alternatively, the change in receptor number may be an important part of the therapeutic response itself. One example is tricyclic antidepressants (Chapter 22); these produce an immediate increase in the availability of monoamine neurotransmitters, but the therapeutic response is associated with a subsequent, adaptive downregulation in monoamine receptor numbers occurring over several weeks.

# PROPERTIES OF DRUG ACTION

Drug actions can show a number of important properties:

- dose–response relationship,
- selectivity,
- potency,
- efficacy.

## DOSE–RESPONSE RELATIONSHIPS

Using a purified preparation of a single drug, it is possible to define accurately and reproducibly the relationship between the doses of drug administered (or concentrations applied) and the biological effects (responses) at each dose. The results for an individual drug can be displayed on a dose–response curve. In many biological systems, the typical relationship between an increasing drug dose (or concentration in plasma) and the biological response is a hyperbola, with the response curve rising with a gradually diminishing slope to a plateau, which represents the maximal biological response. Plotting instead the logarithm of the dose (or concentration) against the response (plotted on a linear scale) generates a sigmoid (S-shaped) curve. The sigmoid shape of the curve provides a number of advantages for understanding the relationship between drug dose and response: a very wide range of doses can be accommodated easily on the graph, the maximal response plateau is clearly defined, and the central portion of the curve (between about 15% and 85% of maximum) approximates to a straight line, allowing the collection of fewer data points to delineate the relationship accurately.

Fig. 1.11 shows the log dose–response relationship between a drug and responses it produces at two types of adrenoceptors. In each case, the upward slope of the curve to the right reflects the chemical law that a greater number of reversible molecular interactions of a drug (D) with its receptor (R), due in this case to increasing drug dose, leads to more intracellular signalling by active drug–receptor complexes (DR) and hence a greater response of the cell or tissue (within biological limits). This principle is diametrically opposed to the principle of homeopathy, which argues that serially diluting a drug solution until essentially no drug molecules remain enhances its activity, a belief that is not supported theoretically or experimentally.

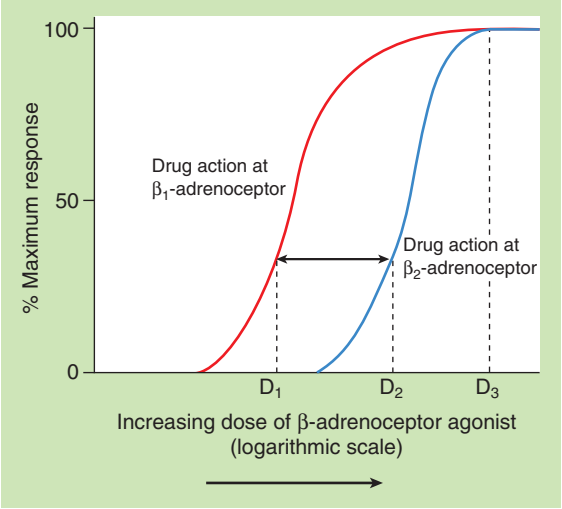


***Fig. 1.11*** **Dose–response relationship and receptor selectivity.** Each curve shows the responses (expressed as percentage of maximum on a linear vertical axis) produced by a hypothetical β-adrenoceptor agonist drug at a range of doses shown on a logarithmic horizontal axis. Plotting the logarithmic dose allows a wide range of doses to be shown on the same axes and transforms the dose–response relationship from a hyperbolic curve to a sigmoid curve, in which the central portion is close to a straight line. The two curves illustrate the relative selectivity of the same drug for the $\beta_1$-adrenoceptor compared with the $\beta_2$-adrenoceptor. At most doses the drug produces $\beta_1$-adrenoceptor stimulation with less effect on $\beta_2$-adrenoceptors. If dose $D_1$ is 10 times lower than dose $D_2$, the selectivity of the drug for the $\beta_1$-adrenoceptor is 10-fold higher. This selectivity diminishes at the higher end of the log dose–response curve and is completely lost at a dose ($D_3$) that produces a maximum response on both $\beta_1$- and $\beta_2$-adrenoceptors.

## Selectivity

As drugs may act preferentially on particular receptor types or subtypes, such as $\beta_1$- and $\beta_2$-adrenoceptors, it is important to be able to quantify the degree of selectivity of a drug. For example, it is important in understanding the therapeutic efficacy and unwanted effects of the bronchodilator drug salbutamol to recognise that it is approximately 10 times more effective in stimulating the $\beta_2$-adrenoceptors in the airway smooth muscle than the $\beta_1$-adrenoceptors in the heart.

In pharmacological studies, selectivity is likely to be investigated by measuring the effects of the drug in vitro on different cells or tissues, each expressing only one of the receptors of interest. Comparison of the two log dose–response curves in Fig. 1.11 shows that for a given response, smaller doses of the drug being tested are required to stimulate the $\beta_1$-adrenoceptor compared with those required to stimulate the $\beta_2$-adrenoceptor; the drug is therefore said to have selectivity of action at the $\beta_1$-adrenoceptor. An example might be dobutamine, which is used to selectively stimulate $\beta_1$-adrenoceptors on the heart in heart failure. The degree of receptor selectivity is given by the ratio of the doses of the drug required to produce a given level of response via each receptor type. It is clear from Fig. 1.11 that the ratio is highly dose-dependent and that the selectivity disappears at extremely high drug doses, because the dose then produces the maximal response of which the biological tissue is capable.

## Potency

The potency of a drug in vitro is largely determined by the strength of its binding to the receptor, which is a reflection of the receptor affinity, and by the inherent ability of the drug/receptor complex to elicit downstream signalling events. The more potent a drug, the lower the concentration needed to give a specified response. In Fig. 1.12, drug $A_1$ is more potent than drug $A_2$ because it produces a specified level of response at a lower concentration. It is important to recognise that potencies of different drugs are compared using the doses required to produce (or block) the *same response* (often chosen arbitrarily as 50% of the maximal response). The straight-line portions of log dose–response curves are usually parallel for drugs that share a common mechanism of action, so the potency ratio is broadly the same at most response values – for example, 20%, 50% or 80%, but not at 100% response. A drug concentration sufficient to produce half of the greatest response achievable by that

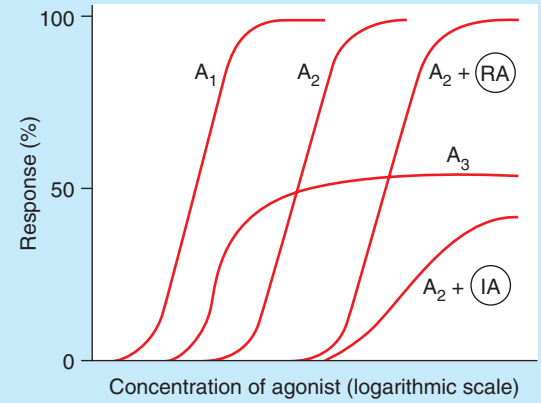


***Fig. 1.12*** **Concentration–response curves for agonists in the absence and presence of competitive and noncompetitive antagonists.** Responses are plotted at different concentrations of two different full agonists ($A_1$ being more potent than $A_2$) and also a partial agonist ($A_3$), which is unable to produce a maximal response even at high concentrations. Responses are also shown for the full agonist $A_2$ in the presence of a fixed concentration of a competitive (reversible) antagonist (RA) or a fixed concentration of a noncompetitive (irreversible) antagonist (IA). The competitive antagonist reduces the potency of agonist $A_2$ (the curve is shifted parallel to the right), but high concentrations of $A_2$ are able to surmount the effects of the competitive antagonist and produce a maximal response. A noncompetitive antagonist reduces agonist activity either by irreversibly blocking the agonist binding site, or by changing its conformation by binding reversibly or irreversibly at an allosteric site. Unlike competitive antagonists, a noncompetitive antagonist reduces the maximal response even at high agonist concentrations, as shown in the curve $A_2$ + IA compared with $A_2$ alone.

drug is described as its $EC_{50}$ (the effective concentration for 50% of the maximal response). The $EC_{50}$ (or $ED_{50}$ if drug *dose* is considered) is a convenient way to compare the potencies of similar drugs; the lower the $EC_{50}$ (or $ED_{50}$), the more potent the drug.

In vivo the potency of a drug, defined as the dose of the drug required to produce a desired clinical effect, depends not only on its affinity for the receptor, the receptor number and the efficiency of the stimulus–response mechanism, but also on pharmacokinetic variables that determine the delivery of the drug to its site of receptor action (Chapter 2). Therefore the relative potencies of related drugs in vivo may not directly reflect their in vitro receptor-binding properties.

## Efficacy

The efficacy of a drug is its ability to produce the maximal response possible for a particular biological system and relates to the extent of functional change that can be imparted to the receptor by the drug, based on its affinity for the receptor and its ability to induce receptor signalling (discussed later). Drug efficacy is arguably of greater clinical importance than potency because a greater therapeutic benefit may be obtained with a more efficacious drug, while a more potent drug may merely allow a smaller dose to be given for the same clinical benefit. In turn, efficacy and potency need to be balanced against drug toxicity to produce the best balance of benefit and risk for the patient. Drug toxicity and safety are discussed in Chapters 3 and 53.

# TYPES OF DRUG ACTION

Drugs can be classified by their receptor action as:

- agonists,
- antagonists,
- partial agonists,
- inverse agonists,
- allosteric modulators,
- enzyme inhibitors or activators,
- nonspecific,
- physiological antagonists.

## AGONISTS

An agonist, whether a therapeutic drug or an endogenous ligand, binds to the receptor or site of action and changes the conformation of the receptor to its active state, leading to signalling via second messenger pathways. An agonist shows both *affinity* (the strength of binding for the receptor) and *intrinsic activity* (the extent of conformational change imparted to the receptor leading to receptor signalling). Drugs differ in their affinity and intrinsic activity at the same receptor, as well as between different receptors.

Agonists are traditionally divided into two main groups (Fig. 1.12):

- full agonists (curves $A_1$ and $A_2$), which give an increase in response with an increase in concentration until the maximum possible response is obtained for that system;
- partial agonists (curve $A_3$), which also give an increase in response with increase in concentration, but cannot produce the maximum possible response in the system.

The reasons for this difference, and also a third group of agonists (inverse agonists), are described as follows.

## Affinity and intrinsic activity

The affinity of a drug is related to the aggregate strength of the atomic interactions between the drug molecule and its receptor site of action, which determines the relative rates of drug binding and dissociation. The higher the affinity, the lower the drug concentration required to occupy a given fraction of receptors. Affinity therefore determines the drug concentration necessary to produce a certain response and is directly related to the potency of the drug. In Fig. 1.12, drug $A_1$ is more potent than drug $A_2$, but both are capable of producing a maximal response (they have the same efficacy as they are full agonists).

Intrinsic activity describes the ability of the bound drug to induce the conformational changes in the receptor that induce receptor signalling. Although affinity is a prerequisite for binding to a receptor, a drug may bind with high affinity but have low intrinsic activity. A drug with zero intrinsic activity is an antagonist (as discussed later).

It should be noted that the rate of binding and rate of dissociation of a reversible drug at its receptor are of negligible importance in determining its rate of onset or duration of effect in vivo, because these depend mainly on the rates of delivery of the drug to, and removal from, the target organ; that is, on the overall absorption, distribution and elimination rates of the drug from the body (Chapter 2).

## Spare receptors

Some full agonists that have relatively low intrinsic activity may have to occupy all of the available receptors to produce a maximal response. However, many full agonists have sufficient affinity and intrinsic activity that the maximal response can be produced even though many receptors remain unoccupied; that is, there may be *spare receptors* (or a *receptor reserve*). The concept of spare receptors does not imply a distinct pool of permanently redundant receptors, only that a proportion of the receptor population is unoccupied at a particular point in time. Spare receptors may function to enhance the speed of cellular response, because an excess of available receptors reduces the distance and therefore the time that a ligand molecule needs to diffuse to find an unoccupied receptor; an example is the excess of acetylcholine nicotinic $N_2$ receptors that contributes to fast synaptic transmission in the neuromuscular junction (Chapter 27).

The concept of spare receptors is also helpful when considering changes in receptor numbers during chronic treatment, particularly receptor downregulation. As maximal responses are often produced at drug concentrations that do not attain 100% receptor occupancy, the same maximal response may still be produced when receptor numbers are downregulated, but only with higher percentage occupancy of the reduced number of receptors. If receptors are downregulated still further, the number remaining may be insufficient to generate a maximal response. Receptor downregulation may therefore contribute to a decline in responsiveness to some drugs during chronic treatment (drug tolerance).

## ANTAGONISTS

Pharmacological antagonists (often called 'blockers') reduce the activity of an agonist at the same receptor, and can be contrasted with physiological antagonists (discussed later) that act at another type of receptor or at other sites of action to oppose the physiological response to the agonist. Pharmacological antagonists can be competitive (surmountable) or noncompetitive (nonsurmountable).

A *competitive* antagonist binds reversibly to the ligand binding site of a receptor, either alone or in competition with a drug agonist or natural ligand. It therefore must have affinity for the ligand binding site (which may be as high as that of any agonist), but it has zero intrinsic activity. It therefore cannot cause the conformational change that converts the receptor to its active state and induces intracellular signalling. The antagonist will, however, competitively impair access of agonist molecules to the ligand binding site and thereby reduce receptor activation. The presence of a competitive antagonist may only be detectable by its impairment of agonist activity, and the extent of antagonism will depend on the relative amounts of agonist and antagonist. For example, $\beta_1$-adrenoceptor antagonists lower the heart rate markedly only when it is already elevated by endogenous agonists such as adrenaline and noradrenaline. The reversible binding of competitive antagonists means that the receptor blockade can be overcome (surmounted) by an increase in the concentration of an agonist. Therefore competitive antagonist drugs move the dose–response curve for an agonist in a parallel fashion to the right but do not alter the maximum possible response at high agonist concentrations (as shown in curve $A_2$ + RA when compared with $A_2$ alone in Fig. 1.12).

*Noncompetitive* antagonists either bind to the receptor irreversibly (covalently) at the ligand binding site, denying access to the agonist, or they change the conformation of the receptor by binding reversibly or irreversibly at another (allosteric) site, producing conformational changes that impede the ability of the agonist to access its binding site or block the conformational changes in the receptor needed for intracellular signalling. In either case, the effects of noncompetitive antagonists cannot be negated (surmounted) by competition from the agonist, so they reduce the magnitude of the maximum response that can be produced by any concentration of agonist (as shown by curve A2 + IA in Fig. 1.12). A noncompetitive antagonist will also cause a rightward shift of the agonist log dose–response curve if there is no reserve of spare receptors.

Like agonists, antagonists exhibit varying degrees of selectivity of action. For example, phenoxybenzamine is an antagonist which blocks the ligand binding site of $\alpha$-adrenoceptors, but not that of $\beta$-adrenoceptors. Conversely, propranolol is an antagonist of $\beta$-adrenoceptors, but not $\alpha$-adrenoceptors. Bisoprolol is further selective for the $\beta_1$-adrenoceptor subtype, and has less blocking action at $\beta_2$-adrenoceptors (or $\alpha$-adrenoceptors).

## PARTIAL AGONISTS

An agonist that is unable to produce a maximal response is a partial agonist (e.g. drug $A_3$ in Fig. 1.12). Even maximal occupancy of all available receptors produces only a submaximal response due to low intrinsic activity of the partial agonist, for example because of incomplete amplification of the receptor signal via the G-proteins. Despite their name, partial agonists can be considered to have both agonist and antagonist properties, depending on the presence and type of other ligands. A partial agonist usually shows weak agonist activity in the absence of another ligand, and such partial agonism can be blocked by an antagonist. But in the presence of a full agonist, a partial agonist will behave as a weak antagonist because it prevents access to the receptor of a molecule with higher intrinsic ability to initiate receptor signalling; this results in a reduced response. Partial agonism is responsible for the therapeutic efficacy of several drugs, including buspirone, buprenorphine, pindolol and salbutamol. These drugs can act as stabilisers of the variable activity of the natural ligand, as they enhance receptor activity when the endogenous ligand levels are low or zero, but block receptor activity when endogenous ligand levels are high.

## INVERSE AGONISTS

The previously provided definitions of agonists, partial agonists and antagonists reflect the classical model of

drug–receptor interactions, in which an unoccupied receptor has no signalling activity. It is now recognised that many GPCRs show constitutive signalling independently of an agonist. Inverse agonists were first recognised when some compounds were found to show negative intrinsic activity: they acted alone on unoccupied receptors to produce a change opposite to that caused by an agonist. Inverse agonists shift the receptor equilibrium towards the inactive state, thereby reducing the level of spontaneous receptor activity. An inverse agonist can be distinguished from the typical antagonists discussed previously, which, on their own, bind to the receptor without affecting receptor signalling, as they have zero intrinsic activity ('neutral' or 'silent' antagonists). The action of a neutral antagonist depends on depriving the access of agonists to the receptor; a neutral antagonist can therefore block the effects of either a positive or inverse agonist at a receptor with spontaneous signalling activity.

The role of inverse agonism in the therapeutic effects of drugs remains to be fully elucidated, but a number of drugs exhibit this type of activity (Table 1.5). The same drug may even show a mixed pattern of full or partial agonism, inverse agonism or antagonism at different receptors. Some drugs (e.g. some β-adrenoceptor antagonists) can act as neutral antagonists at a receptor in one tissue and as inverse agonists when the same receptor is expressed in a different tissue, probably due to association of the receptor with different G-proteins.

## ALLOSTERIC MODULATORS

Allosteric modulation has been described previously in the context of one type of noncompetitive antagonist, which does not compete directly with an agonist for access to the ligand binding site (also called the orthosteric site), but binds to a different (allosteric) site. Allosteric modulation changes receptor activity by altering the conformation of the orthosteric binding site or of sites involved in intracellular signalling. Allosteric modulators can also enhance the binding of the natural ligand or other drugs to the receptor or enhance their propensity to induce receptor signalling. In some cases, an allosteric modulator may not bind to the allosteric site (or only bind poorly) in the absence of the agonist, but its allosteric binding increases when binding of the agonist to the orthosteric site alters receptor conformation. An example of allosteric modulators is the family of benzodiazepine anxiolytic drugs, which allosterically alter the affinity of chloride channels for the neurotransmitter ligand GABA and enhance its inhibitory activity on neurons (Chapter 20).

**Table 1.5 Examples of drugs with inverse agonist activity**

| Receptor | Drugs |
|---|---|
| $\alpha_1$-Adrenoceptor | Prazosin, terazosin |
| $\beta_1$-Adrenoceptor | Metoprolol, carvedilol, propranolol |
| Angiotensin II receptor ($AT_1$) | Losartan, candesartan, irbesartan |
| Cysteinyl-leukotriene ($CysLT_1$) | Montelukast |
| Dopamine ($D_2$) | Haloperidol, clozapine, olanzapine |
| Histamine ($H_1$) | Cetirizine, loratadine |
| Histamine ($H_2$) | Cimetidine, ranitidine, famotidine |
| Muscarinic ($M_1$) | Pirenzepine |
| Opioid (μ, MOR) | Naloxone |

## ENZYME INHIBITORS AND ACTIVATORS

The site of action of many drugs is an enzyme, which may be an intracellular or cell-surface enzyme or one found in plasma or other body fluids. Such drugs act reversibly or irreversibly either on the catalytic site or at an allosteric site on the enzyme to modulate its catalytic activity; most often the effect is inhibition, and important examples of enzyme inhibitors are shown in Table 1.4. An example of an enzyme activator is heparin, which enhances the activity of antithrombin III, a protease that regulates the activity of the coagulation pathway.

## NONSPECIFIC ACTIONS

A few drugs produce their desired therapeutic outcome without interaction with a specific site of action on a protein; for example, the diuretic mannitol exerts an osmotic effect in the lumen of the kidney tubule, which reduces reabsorption of water into the blood (Chapter 14).

## PHYSIOLOGICAL ANTAGONISTS

Physiological antagonism is said to occur when a drug has a physiological effect opposing that of an agonist but without binding to the same receptor. The increase in heart rate produced by a $\beta_1$-adrenoceptor agonist, an effect which mimics the action of the sympathetic autonomic nervous system, can be blocked pharmacologically with an antagonist at $\beta_1$-adrenoceptors or physiologically by a muscarinic receptor agonist, which mimics the opposing (parasympathetic) autonomic nervous system. The site of action of the physiological antagonist may be on a different cell, tissue or organ than that of the agonist.

# TOLERANCE TO DRUG EFFECTS

Tolerance to drug effects is defined as a decrease in response to repeated doses, often necessitating an increase in dosage to maintain an adequate clinical response. Tolerance may occur through pharmacokinetic changes in the concentrations of a drug available at the receptor or through pharmacodynamic changes at the drug receptor. Pharmacokinetic effects are discussed in Chapter 2; some drugs stimulate their own metabolism, so they are eliminated more rapidly on repeated dosing, and lower concentrations of the drug are available to produce a response.

Most clinically important examples of tolerance arise from pharmacodynamic changes in receptor numbers and in concentration–response relationships. Desensitisation is used to describe both long-term and short-term changes arising

from a decrease in response of the receptor. Desensitisation can occur by a number of mechanisms:

- decreased receptor numbers (downregulation), due to decreased transcriptional expression or receptor internalisation;
- decreased receptor binding affinity;
- decreased G-protein coupling;
- modulation of the downstream response to the initial signal.

GPCRs can show rapid desensitisation (within minutes) during continued activation, which occurs through three mechanisms:

- **Homologous desensitisation.** The enzymes activated following selective binding of an agonist to its receptor–G-protein complex include G protein-coupled receptor kinases (GRKs), which interact with the βγ-subunit of the G-protein and inactivate the occupied receptor protein by phosphorylation; a related peptide, arrestin-2, enhances the GRK-mediated desensitisation of the GPCR and may itself activate distinct cell signalling pathways.
- **Heterologous desensitisation.** Also known as cross-desensitisation, this occurs when an agonist at one receptor causes loss of sensitivity to other agonists. The agonist increases intracellular cAMP which activates protein kinase A or C; these phosphorylate the cross-desensitised receptors (whether occupied or not), and members of the arrestin family prevent them from coupling with G-proteins. Other mechanisms of heterologous desensitisation exist.
- **Receptor internalisation.** Internalisation can occur within minutes when constant activation of a GPCR makes the receptor unavailable for further agonist action by uncoupling the G-protein from the receptor. The phosphorylated receptor protein is endocytosed and may undergo intracellular dephosphorylation prior to re-entering the cytoplasmic membrane.

Downstream modulation of the signal may also occur through feedback mechanisms or simply through depletion of some essential cofactor. An example of the latter is the depletion of the thiol (-SH or sulphydryl) groups necessary for the generation of nitric oxide during chronic administration of organic nitrates (Chapter 5).

## GENETIC VARIATION IN DRUG RESPONSES

Biological characteristics, including responses to drug administration, vary among individuals, and genetic differences can contribute to these inter-individual variations. For most drugs, the nature of the response is broadly similar in different individuals, but the magnitude of the response to the same dose can differ markedly, at least partly due to genetic factors. Such variability creates the need to individualise drug dosages for different people.

Drug responses may follow a unimodal (Gaussian) distribution, reflecting the sum of many small genetic variations in receptors, enzymes or transporters that respond to or handle the drug (Fig. 1.13A). Genetic variation may also give rise to discrete subpopulations of individuals in which a drug shows distinctly different responses (see Fig. 1.13B), such that some individuals may have no response to a standard dose, while others show toxicity. Understanding genetic variation is of increasing importance in drug development (see Chapter 3) because it allows the possibility of genetic

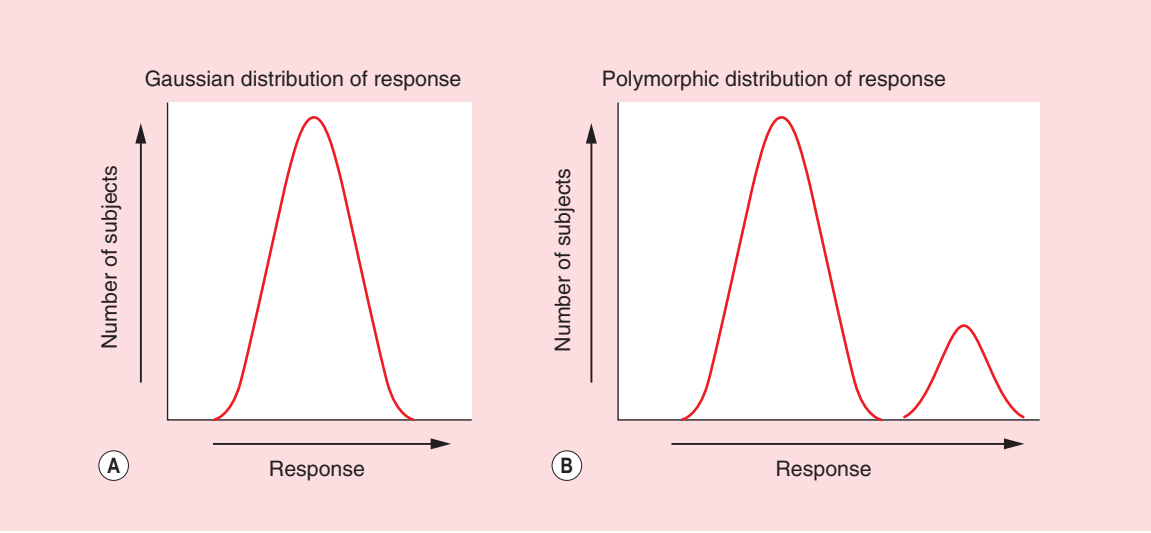


***Fig. 1.13*** **Inter-individual variation in response.** The graphs show the numbers of individual subjects in a population plotted against their varying levels of response to a single dose of a drug. (A) In the unimodal distribution most individuals show a middling response and the overall shape is a normal (Gaussian) distribution. Part of this variability may result from polymorphism in multiple genes encoding drug receptors and proteins involved in the drug's absorption and elimination. (B) The bimodal distribution shows discrete responder and nonresponder subgroups, possibly due to a single genetic polymorphism in a drug receptor or drug-metabolising enzyme.

screening to optimise drug and dosage selection (personalised or individualised medicine).

*Pharmacogenetics* has been defined as the study of genetic variation that results in differing responses to drugs. Such variation may arise from genetic factors that alter the structure, expression or regulation of drug targets (pharmacodynamic effects) or that change the metabolic fates of drugs in the body, usually by altering proteins involved in their absorption, distribution or elimination (pharmacokinetic effects, discussed in Chapter 2). Pharmacogenetic research has been undertaken for many decades, largely in relation to variability in vivo, and has often used classic genetic techniques such as studies of patterns of inheritance in twins.

*Pharmacogenomics* has been defined as the investigation of variation in DNA and RNA characteristics related to drug response, and the term refers mainly to genome-wide approaches that define the presence of single-nucleotide polymorphisms (SNPs) which affect the activity of the gene product. Molecular biological techniques have predicted more than 3 million SNPs in the human genome. SNPs can be:

- in the upstream regulatory sequence of a coding gene, which can result in increased or decreased expression of the gene product (this product remains identical to the normal or 'wild-type' gene product);
- in the coding region of the gene resulting in a gene product with an altered amino acid sequence (this may have higher activity, although this is unlikely; similar activity; lower activity or no activity at all, compared with the wild-type protein);
- inactive, because they are in noncoding or nonregulatory regions of the genome, or, if in a coding region, because the base change does not alter the amino acid encoded, due to the redundancy of the genetic code.

There is still a major challenge in defining the functional consequences of the large numbers of identified SNPs (functional genomics), particularly in the context of combinations of genetic variants (haplotypes). Such studies often require very large numbers of subjects to allow comparison of function in multiple, small haplotype subgroups.

Rapid advances in molecular biology have allowed analysis of interindividual differences in the sequences of many genes encoding drug receptors and proteins involved in drug metabolism and transport. Polymorphism in the latter is likely to have the greatest impact on dosage selection (Chapter 2), while polymorphism in drug targets may be more important in determining the optimal drug for a particular condition. For example, genetic variation in angiotensin $AT_1$ receptors, $\beta_1$-adrenoceptors and $Ca^{2+}$ ion channels may determine the relative effectiveness of angiotensin II receptor antagonists, β-adrenoceptor antagonists (β-blockers) and calcium channel blockers in the treatment of essential hypertension.

In practice, although genetic polymorphism has been reported in many receptor types and these have been a major focus of research in relation to the aetiology of disease, relatively few studies to date have demonstrated a clear influence on drug responses. Common polymorphisms have been identified in the human $\beta_2$-adrenoceptor gene *ADRB2*, and certain variants have been associated with differences in receptor downregulation and loss of therapeutic response in people with asthma while using $\beta_2$-adrenoceptor agonist inhalers (Chapter 12). The clinical response in people with asthma to treatment with leukotriene modulator drugs is influenced by genetic polymorphism in enzymes of the leukotriene (5-lipoxygenase) pathway. Variants in the epidermal growth factor receptor (EGFR), an RTK, have been reported to predict tumour response to the EGFR inhibitor gefitinib in individuals with nonsmall-cell lung cancer. Such examples may support genotyping to target drug treatments to those individuals most likely to respond.

Conversely, pharmacogenetic information may be used to avoid a particular treatment in people likely to experience serious adverse reactions to a specific drug. Variation in human leucocyte antigen (HLA) genes has been associated with adverse skin and liver reactions to several drugs, including abacavir, an antiretroviral drug used in HIV infection.

Compared with pharmacodynamic targets, genetic variation has been more extensively characterised in drug-metabolising enzymes, particularly in cytochrome P450 isoenzymes and others involved in glucuronidation, acetylation and methylation. Gene variations in drug-metabolising enzymes are discussed at the end of Chapter 2. Detailed information on human genotypic variation can be found in the Online Mendelian Inheritance in Man (OMIM) database (www.ncbi.nlm.nih.gov/omim). Therapeutic exploitation of genotypic differences will require specific information about individuals based on detailed genetic testing. Until such genetic information is routinely incorporated in clinical trials, careful monitoring of clinical response will remain the best guide to successful treatment.

## SUMMARY

The therapeutic benefits of drugs arise from their ability to interact selectively with target receptors, most of which are regulatory molecules involved in the control of cellular and systemic functions by endogenous ligands. Drugs may also cause unwanted effects; judging the balance of benefit and risk is at the heart of safe and effective prescribing. Increasing knowledge of the complexity of receptor pharmacology and improvements in drug selectivity offer the promise of safer drugs in the future, especially when information on genetic variation is more routinely available.

## SELF-ASSESSMENT

### True/false questions

1. Clinical pharmacology is the study of drugs that doctors use to treat disease.
2. Drugs act at receptors only on the external surface of cells.
3. Diluting drugs enhances their pharmacological effects.
4. Drugs produce permanent biochemical changes in their receptors.
5. Plotting drug dose (or plasma concentration) against response usually produces a sigmoid curve.
6. The $EC_{50}$ is the concentration of drug that produces a half-maximal response.
7. On a log dose–response plot, the drug with a curve to the right is more potent than a drug with a curve on the left.

8. A receptor antagonist is defined as a drug with zero affinity for the receptor.
9. A competitive antagonist shifts the log dose–response curve of an agonist to the right, without affecting the maximal response.
10. A partial agonist is one that, even at its highest dose, cannot achieve the same maximal response as a full agonist at the same receptor.
11. A full agonist achieves a maximal response when all its receptors are occupied.
12. Changes in receptor numbers can cause tolerance to drug effects.

# ANSWERS

## True/false answers

1. **True**. Clinical pharmacology also deals with drugs used in disease prevention and diagnosis, and in the alleviation of pain and suffering.
2. **False**. While many types of receptors are found in cell membranes, including ion channels, GPCRs and tyrosine kinase receptors, other drug targets, including steroid receptors and many enzymes (e.g. cyclo-oxygenase, PDE), are intracellular and others are humoral, such as thrombin in plasma.
3. **False**. The relationship between the dose or concentration of a drug and the response may be complex but is typically dependent on the number of interactions between the drug molecules and their molecular target, a consequence of the Law of Mass Action, and so are usually greater at higher drug concentrations, within biological limits.
4. **False**. Molecular interactions between most drugs and their receptors are typically transient, and the conformational changes induced in the receptor are reversible; irreversible drugs may act by covalent chemical bonding.
5. **False**. Plotting drug dose or plasma concentration against response typically produces a hyperbola; a sigmoid (S-shaped) curve is produced by plotting the logarithm of dose or concentration against the response.
6. **True**. The $EC_{50}$ (or $ED_{50}$) is the concentration (or dose) effective in producing 50% of the maximal response and is a convenient way of comparing drug potencies.
7. **False.** A drug with its log dose–response curve to the left is the more potent, as it produces a given level of response at a lower dose.
8. **False**. A full ('neutral' or 'silent') antagonist must have affinity to bind to its receptor, but it has zero intrinsic ability to activate the receptor. Partial agonists can also have an antagonist effect in the presence of a full agonist. Receptors with inherent signalling activity, even when unoccupied, can be antagonised by inverse agonists.
9. **True**. A fixed dose of a competitive antagonist shifts the log dose–response curve of the agonist to the right in a parallel fashion; it can be surmounted by increasing the dose of agonist, so that the same maximal response can be achieved.
10. **True**. A partial agonist has low intrinsic ability to induce conformational change in the receptor so it does not elicit a maximal response even with full receptor occupancy.
11. **False**. Many full agonists are able to elicit a maximal response when less than 100% of receptors are occupied; the unoccupied receptors are termed 'spare receptors'.
12. **True**. Tolerance may be caused by desensitisation, internalisation or downregulation of receptors, requiring higher drug doses to maintain the same response. Tolerance also often results from enhanced drug elimination that alters the concentrations of drugs available to interact with the receptor.

### FURTHER READING


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**Examples of cell surface receptor families and their properties**

This is a reference list of members of important families of GPCRs, LGICs and VGICs, many of which are therapeutic drug targets. Examples of agonists and antagonists are also shown; these include endogenous ligands and some drugs not currently in clinical use. For further information see the relevant sections of Alexander, S.P.H., et al., 2015. IUPHAR/BPS concise guide to pharmacology 2015–16. *Br. J. Pharmacol.* 172, 5729–6202 (available at http://guidetopharmacology.org). For examples of important intracellular receptors and enzymes targeted by therapeutic drugs, see Tables 1.2 and 1.4.

| Type | Typical location(s) | Principal transduction mechanism | Major biological actions | Agonists | Antagonists |
|---|---|---|---|---|---|
| G-protein-coupled receptors (GPCRs) | | | | | |
| *Cholinergic* | | | | | |
| *Muscarinic* | | | | | |
| $M_1$ | CNS, salivary, gastric; minor role in autonomic ganglia | $G_q$ | Neurotransmission in CNS, gastric secretion | *Nonselective for all M receptors*: carbachol | Pirenzepine *Nonselective for all M receptors*: atropine, ipratropium, oxybutynin, tolterodine |
| $M_2$ | Heart, CNS | $G_i$ | Bradycardia, smooth muscle contraction (GI tract, airways, bladder) | | |
| $M_3$ | Smooth muscles, secretory glands, CNS | $G_q$ | Contraction, secretion | I | Darifenacin, tiotropium |
| $M_4$ | CNS | $G_i$ | Unclear | | |
| $M_5$ | CNS | $G_q$ | Unclear | | |
| *Adrenergic* | | | | | |
| *α-Adrenoceptors* | | | | | |
| $\alpha_1$ ($\alpha_{1A}$, $\alpha_{1B}$, $\alpha_{1D}$) | CNS, postsynaptic in sympathetic nervous system, human prostate ($\alpha_{1A}$) | $G_q$ | Contraction of arterial smooth muscle, decrease in contractions of gut, contraction of prostate tissue | Phenylephrine, methoxamine, NA ≥ Adr | Prazosin, indoramin (tamsulosin $\alpha_{1A}$) |
| $\alpha_2$ ($\alpha_{2A}$, $\alpha_{2B}$, $\alpha_{2C}$) | Presynaptic (in both α- and β-adrenergic neurons) | $G_i$ | Decreased NA release | Clonidine, Adr > NA (oxymetazoline $\alpha_{2A}$) | Yohimbine |
| *β-Adrenoceptors* | | | | | |
| $\beta_1$ | CNS, heart (nodes and myocardium), kidney | $G_s$ | Increased force and rate of cardiac contraction, renin release | Dobutamine, NA > Adr | Atenolol, metoprololol |
| $\beta_2$ | Bronchial smooth muscle, also widespread | $G_s$ | Bronchodilation, decrease in contraction of gut, glycogenolysis | Salbutamol, salmeterol, terbutaline, Adr > NA | Butoxamine |
| $\beta_3$ | Adipocytes, bladder | $G_s$ | Lipolysis, bladder emptying | Adr = NA | – |
| Cannabinoids | | | | | |
| $CB_1$ | Cortex, hippocampus, amygdala, basal ganglia, cerebellum | $G_{i/o}$ | Behaviour, pain, nausea, stimulation of appetite, addiction, depression, hypotension | Tetrahydrocannabinol, anandamide, 2-arachidonylglycerol | Rimonabant |