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MEDICAL PHARMACOLOGY & THERAPEUTICS

Derek G. Waller
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Andrew W. Hitchings

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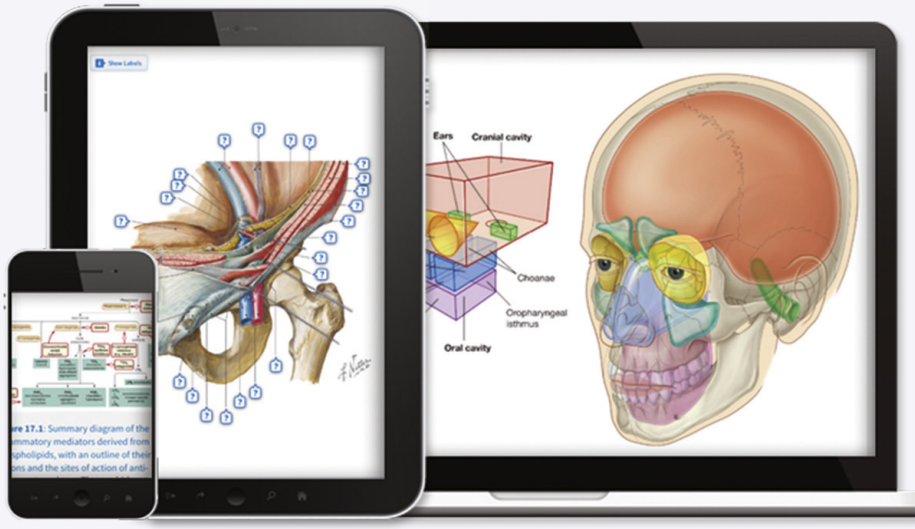

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MEDICAL PHARMACOLOGY & THERAPEUTICS

DEDICATION

To our families

Sixth Edition

MEDICAL PHARMACOLOGY & THERAPEUTICS

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Contents

Preface

The sixth edition of *Medical Pharmacology and Therapeutics* has been revised and updated to build upon the strengths and popular approach of previous editions. Its aim remains to provide a single volume for healthcare professionals and students requiring a sound knowledge of the basic principles of clinical pharmacology combined with the practice of drug prescribing for the management of disease.

Medical Pharmacology and Therapeutics relates key information on basic pharmacology to other relevant biomedical sciences in order to underpin the clinical contexts, and each disease-based chapter is then structured to reflect the ways that relevant drugs are used in clinical practice. The chapters covering generic concepts in pharmacology and therapeutics include sections on drug action at a cellular level, pharmacokinetics, pharmacogenetics, drug development, drug toxicity and the principles of prescribing. The sections on clinical management in each disease area have been thoroughly revised and updated in line with best practice and the relevant national guidelines, including on COVID-19.

Each chapter in this sixth 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 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 covered in depth to illustrate the common pharmacological characteristics of their class and to introduce the reader to those drugs currently in the most widespread clinical use.
- A structured approach to the principles of disease management, outlining the core principles of drug choice and planning a therapeutic regimen for many common diseases.
- Drug compendia at the close of each chapter enable any drug encountered by the reader in day-to-day work or study to be placed within its drug class and its key features related to the example drugs covered in the chapter.
- An expanded section of self-assessment questions for learning and revision of the concepts and content in each chapter, including one-best-answer (OBA), extended-matching-item (EMI), true-false and case scenario-based questions.

It is our intention that the sixth 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, to enable them to evaluate the findings of basic and clinical research, to encourage them to teach and train others in their profession, and to develop the skills of lifelong learning that will enable them to tackle changing healthcare needs and emerging threats.

DGW
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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 Nonproprietary 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.

Principles of Pharmacology and Mechanisms of Drug Action

1

Chapter Outline

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 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 against 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 medical 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; and
- 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 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*), usually shared to variable extents by other drugs in the same class;
- the main clinical effects of the drug and hence the reasons for using it (its *indications*);
- where it fits into the overall therapeutic pathway for that indication (its *place in therapy*);
- 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 *over-the-counter* (OTC) without prescription;
- how the drug is given (*routes of administration*);
- how its effects are quantified and its doses modified if necessary (*therapeutic 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, a ***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 (https://bnf.nice.org.uk) and its equivalent for prescribing in children, the BNFC (https://bnfc.nice.org.uk) contain monographs for all drugs licensed in the UK and they are the key drug references for UK prescribers. They are also available as a mobile device app (iOS and Android) from BNF Publications. Students should become familiar at an early stage with using the BNF for reference. More detailed information on individual drugs (the summaries 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. Although 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 key 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 otherwise 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 described in Chapter 8 (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

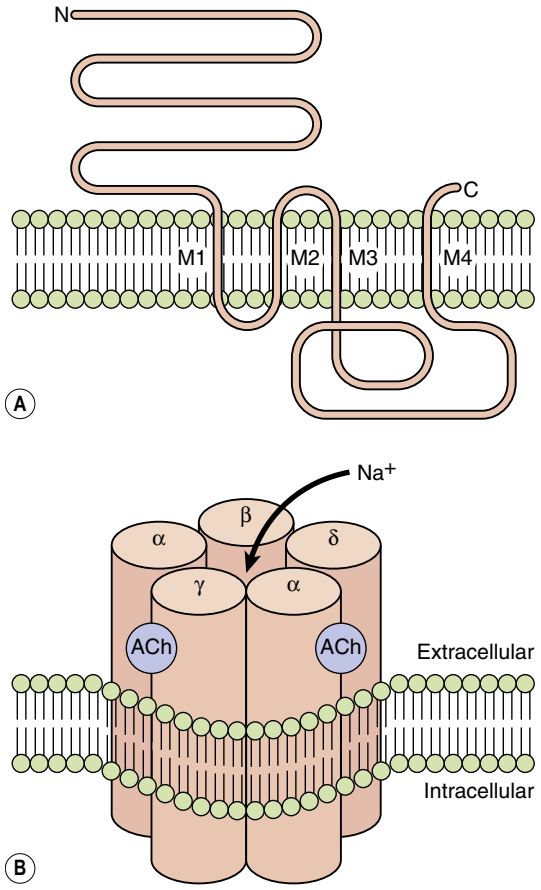

Fig. 1.1 The acetylcholine nicotinic receptor, a typical ligand-gated transmembrane ion channel. (A) The receptor is constructed from subunits with four transmembrane regions (M1–M4). (B) Five subunits are assembled into the ion channel, which has two sites for acetylcholine *(ACh)* binding, each formed 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. *C*, Carboxyl terminus; *N*, amino terminus.

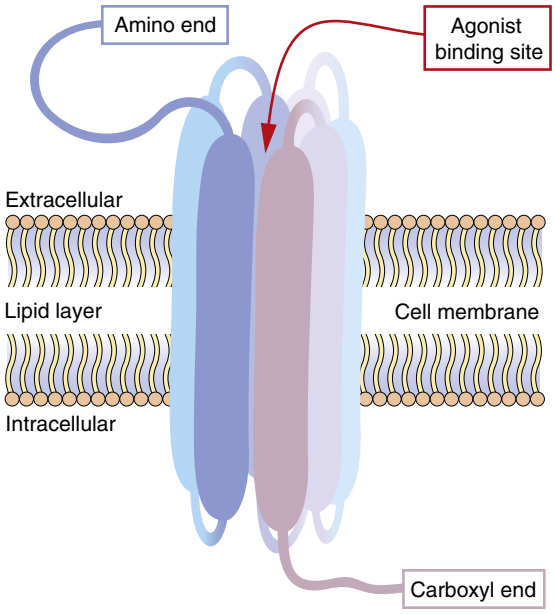

Fig. 1.2 Hypothetical seven-transmembrane (7TM) receptor. The 7TM receptor is a single polypeptide chain with its amino (N-) terminus outside the cell membrane and its carboxyl (C-) terminus inside the cell. The chain is folded such that it crosses the membrane seven times, with each hydrophobic transmembrane 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.

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 then inactivated by acetylcholinesterase. 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 (see Chapter 18). Drugs may also modulate 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 β_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 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 (G-protein–coupled receptor).

The G-protein system

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

- **The α-subunit.** Eighteen different types have been identified, belonging to four families (α_s, α_i, α_q and $\alpha_{12/13}$). The α-subunit is important because it binds guanosine 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, a process that is accelerated by GTPase-activating proteins (GAP).
- **The βγ-complex.** There are 5 isoforms of β-subunit and 12 isoforms of γ-subunit 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),

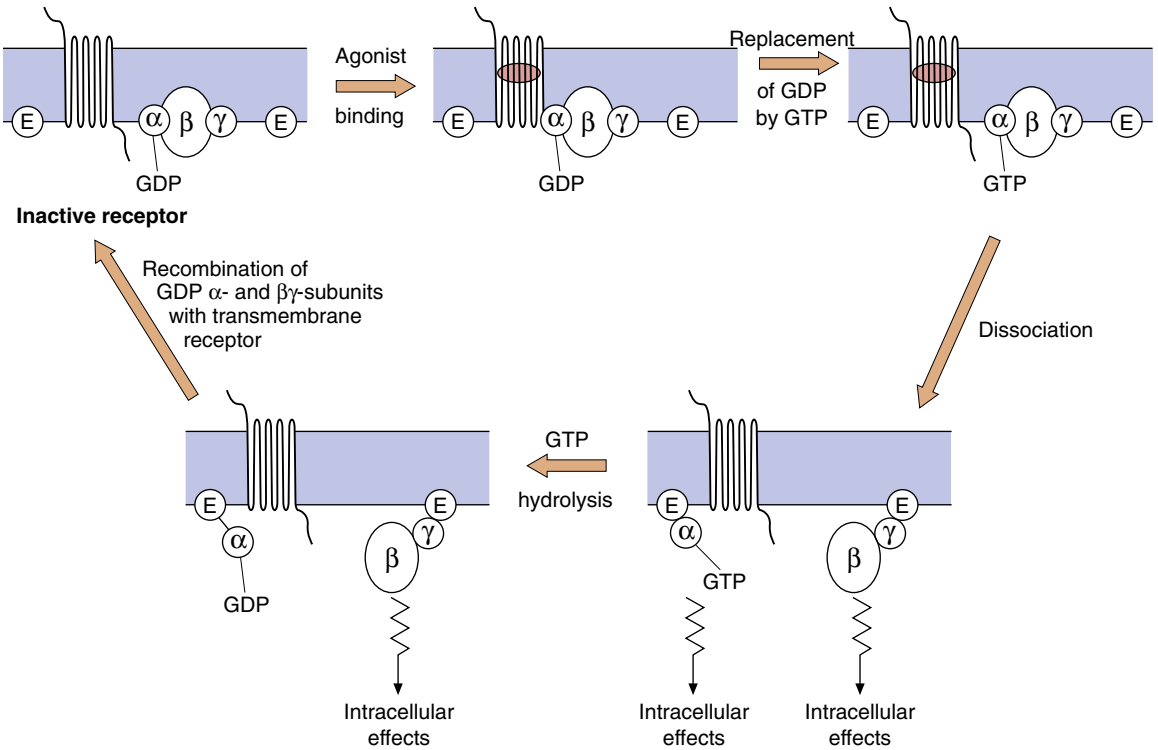

Fig. 1.3 The functioning of G-protein subunits. Ligand (agonist) binding results in replacement of guanosine diphosphate *(GDP)* on the α-subunit by guanosine triphosphate *(GTP)* and the dissociation of the α- and βγ-subunits, each of which can affect a range of intracellular systems (shown as *E* in 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.

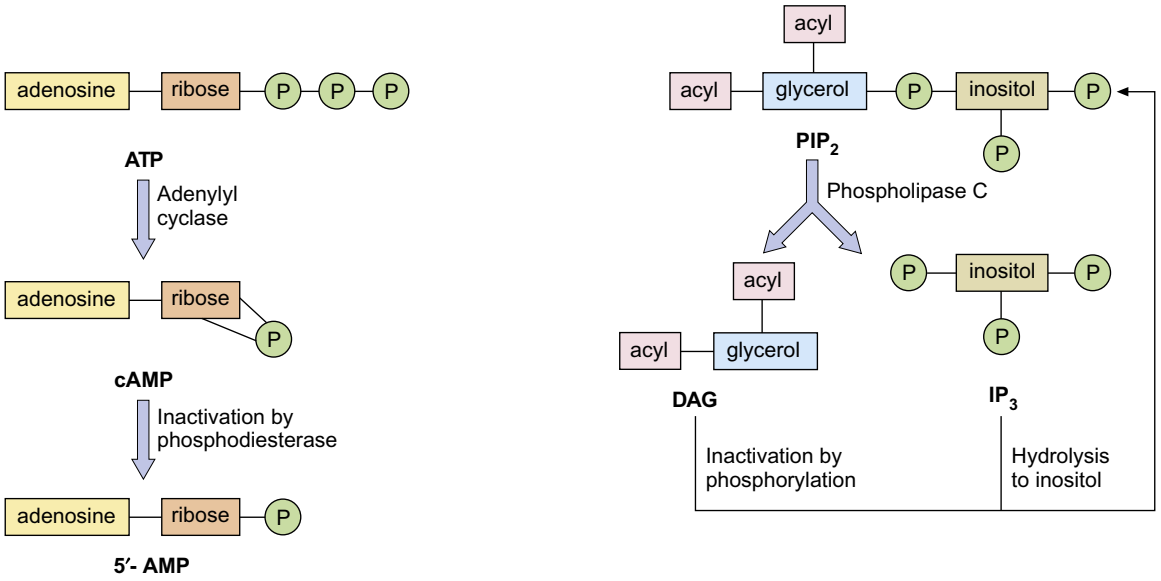

Fig. 1.4 Second messenger systems. Stimulation of G-protein–coupled receptors produces intracellular changes by activating or inhibiting cascades of second messengers. Examples are cyclic adenosine monophosphate *(cAMP)*, and diacylglycerol *(DAG)* and inositol triphosphate *(IP_3)* formed from phosphatidylinositol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

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 in mammals; 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 12 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), which are synthesised from the membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2) by phospholipase C (see Fig. 1.4). There is 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 can 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_α, G_β and G_γ proteins may provide 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

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 Cilostazol Dipyridamole Enoximone Milrinone	Asthma (Chapter 12) Congestive heart failure (Chapter 7) Peripheral vascular disease (Chapter 10)
PDE4	cAMP	Sertoli cells, endothelial cells, kidney, brain, heart, liver, lung, inflammatory cells	Aminophylline Roflumilast	Asthma, COPD (Chapter 12) Inflammation IBD?
PDE5	cGMP	Smooth muscle, endothelium, neurons, lung, platelets	Sildenafil Tadalafil Vardenafil Dipyridamole	Erectile dysfunction (Chapter 16) Pulmonary hypertension (Chapter 6)
PDE6	cGMP	Photoreceptors, pineal gland	Sildenafil (weak)	Undefined
PDE7	cAMP	Skeletal muscle, heart, kidney, brain, pancreas, spinal cord, T-lymphocytes	–	Inflammation (combined with PDE4 inhibitor)? 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
PDE12	cAMP and oligoadenylates	Many tissue sites	–	Undefined

Selective inhibitors of some PDE isoenzymes are shown; methylxanthines such as caffeine, theophylline and theobromine are nonselective inhibitors of multiple PDE isoenzymes.
cAMP, Cyclic adenosine monophosphate; *cGMP*, cyclic guanosine monophosphate; *COPD*, chronic obstructive pulmonary disease; *IBD*, inflammatory bowel disease, *PDE*, phosphodiesterase.

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 (see 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 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,

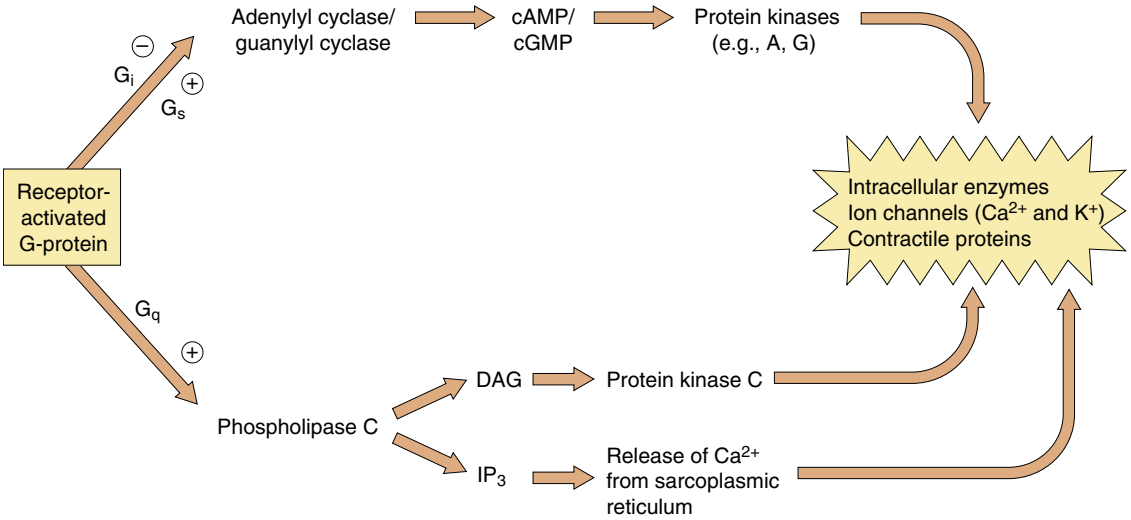

Fig. 1.5 The intracellular consequences of receptor activation. The second messengers, cyclic adenosine monophosphate *(cAMP)*, cyclic guanosine monophosphate *(cGMP)*, diacylglycerol *(DAG)* and inositol 1,4,5-triphosphate *(IP_3)*, produce a number of intracellular changes, either directly or indirectly 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.

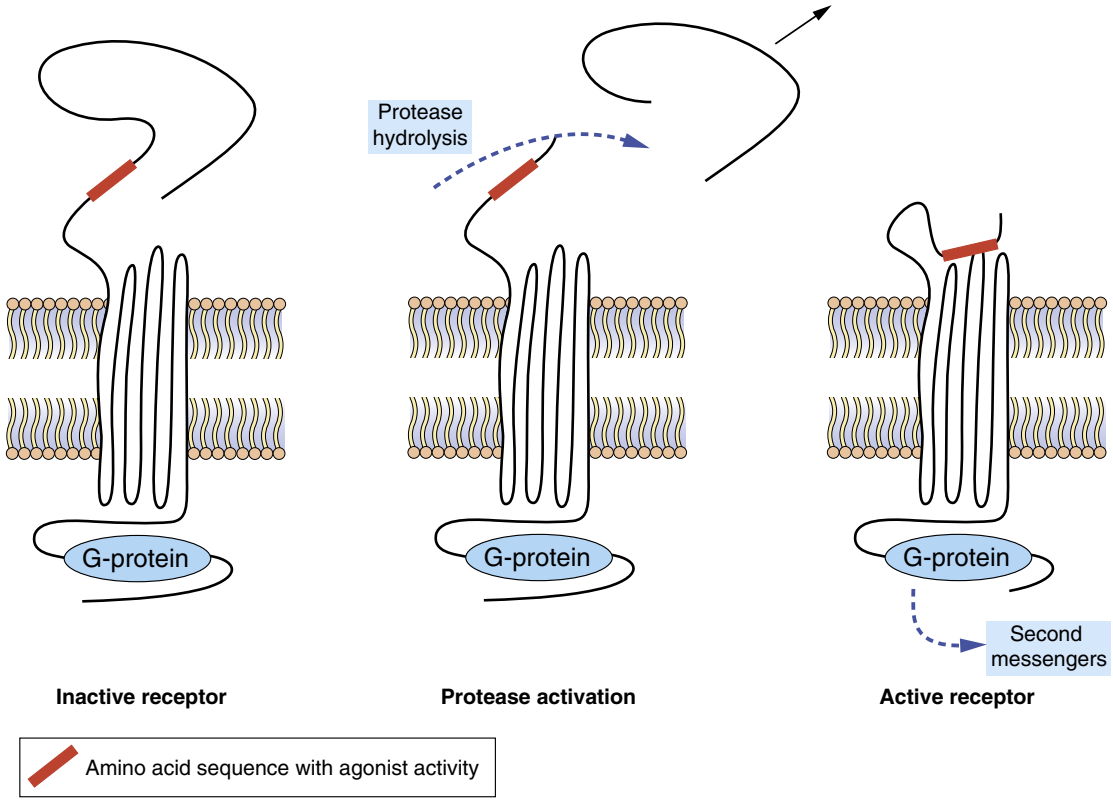

Fig. 1.6 Protease-activated receptors. These G-protein–coupled receptors are activated by proteases such as thrombin which hydrolyse the extracellular peptide chain to expose a segment that acts as a tethered ligand (shown in red) and activates the receptor. The receptor is inactivated by phosphorylation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

leading to effects on gene transcription, apoptosis and cell division. Several RTKs are the targets of anticancer drugs, including trastuzumab, an inhibitor of HER-2 (human epidermal growth factor receptor-2), used in metastatic breast cancer (see Chapter 52).

- *Tyrosine phosphatase receptor family.* These dephosphorylate tyrosines on other transmembrane receptors or cytoplasmic proteins; they are particularly common in immune cells. Ranibizumab is a vascular endothelial growth factor inhibitor, a receptor-linked tyrosine phosphatase, used for the treatment

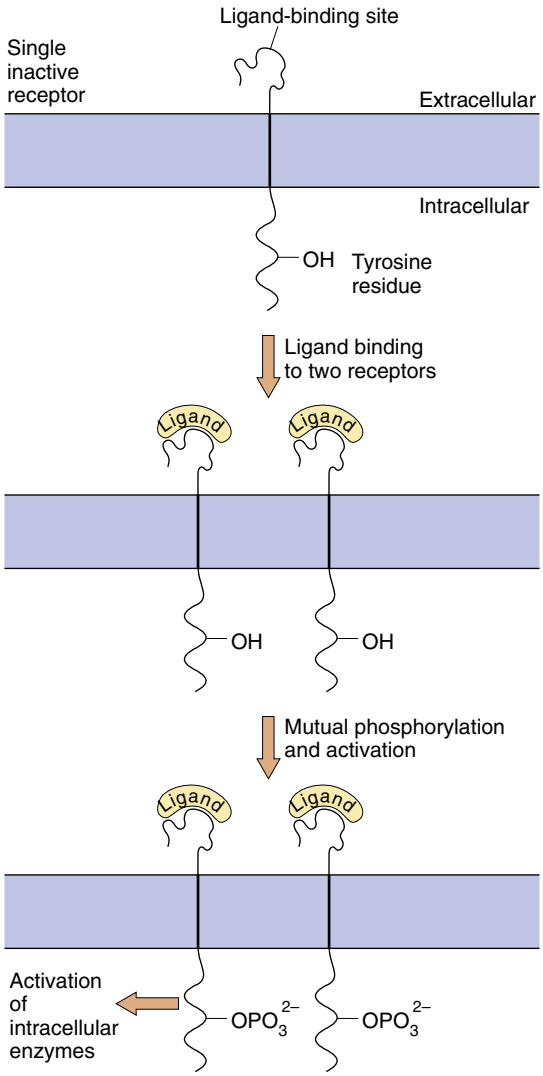

Fig. 1.7 Enzyme-linked transmembrane receptors. This receptor tyrosine kinase has a large extracellular domain, a single transmembrane segment and an integral kinase domain. Ligand binding causes phosphorylation of tyrosine residues on the receptor and on other target proteins, leading to intracellular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

of age-related macular degeneration of the retina (see Chapter 50).

- *Tyrosine kinase–associated receptor family (or non–receptor 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. Imatinib is an inhibitor of ABL and other non–receptor tyrosine kinases (nRTK) and is used in treatment of chronic myeloid leukaemia (see Chapter 52).
- *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.

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 ($\alpha_{1,2,3}$, $\beta_{1,2,3}$)
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, $\gamma_{1,2,3}$)

- *Receptor guanylyl cyclase family.* Members of this family catalyse the formation of cGMP from GTP via a cytosolic domain; linaclotide is a guanylate cyclase 2C receptor agonist used in irritable bowel syndrome.

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 homo/heterodimeric intracellular receptors (Table 1.2) either located in the cytoplasm but capable of translocating to the nucleus (types 1 and 3) or retained within the nucleus (type 2).

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.

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 (HRE) 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
F	C-terminal domain	Highly variable; facilitates homo- or heterodimerisation

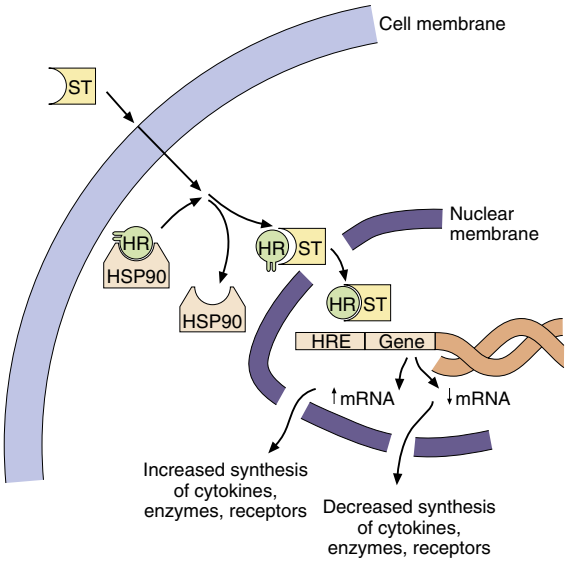

Fig. 1.8 The activation of intracellular hormone receptors. Steroid hormones *(ST)* are lipid-soluble compounds which readily cross cell membranes and bind to their intracellular receptors *(HR)*. This binding displaces a chaperone protein called heat-shock protein *(HSP90)* and the hormone–receptor 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.

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 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 (see Chapter 29), and regulate the expression of genes that influence metabolic events.

Intracellular receptors are the molecular targets of 10% to 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 (see 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), whereas 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

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 (ATIII enhancers) (Chapter 11)	Enoxaparin, dalteparin
Carbonic anhydrase	Carbonic anhydrase inhibitors (Chapters 14, 50)	Acetazolamide
Coagulation factor Xa	Direct oral inhibitors of Factor Xa (Chapter 11)	Rivaroxaban
Cyclo-oxygenase (COX)-1	Nonsteroidal antiinflammatory 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
HMG-CoA reductase	Statins (HMG-CoA reductase inhibitors) (Chapter 48)	Atorvastatin, rosuvastatin, 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 oral 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

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 (see Chapter 14);
- the reuptake of neurotransmitters into nerve terminals by a number of transporters selectively blocked by classes of antidepressant drugs (see 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 (prodrugs) that are enzymatically activated (see 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 α_4-integrin component of vascular cell adhesion molecule (VCAM)-1 and is used to inhibit the autoimmune activity of lymphocytes in relapsing-remitting multiple sclerosis (see Chapter 25). 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 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