

# Medical Pharmacology at a Glance

**Seventh Edition**

**Michael J. Neal**



 **WILEY-BLACKWELL**

# Medical Pharmacology at a Glance

**Michael J. Neal**

Emeritus Professor of Pharmacology  
King's College London  
London

**Seventh Edition**

 **WILEY-BLACKWELL**  
A John Wiley & Sons, Ltd., Publication

This edition first published 2012 © 2012 by John Wiley & Sons, Ltd.

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

*Registered office:* John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

*Editorial offices:* 9600 Garsington Road, Oxford, OX4 2DQ, UK  
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK  
111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at [www.wiley.com/wiley-blackwell](http://www.wiley.com/wiley-blackwell)

The right of the author to be identified as the author of this work has been asserted in accordance with the UK Copyright, Designs and Patents Act 1988.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by the UK Copyright, Designs and Patents Act 1988, without the prior permission of the publisher.

Designations used by companies to distinguish their products are often claimed as trademarks. All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The publisher is not associated with any product or vendor mentioned in this book. This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold on the understanding that the publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

The contents of this work are intended to further general scientific research, understanding, and discussion only and are not intended and should not be relied upon as recommending or promoting a specific method, diagnosis, or treatment by physicians for any particular patient. The publisher and the author make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of medicines, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each medicine, equipment, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. Readers should consult with a specialist where appropriate. The fact that an organization or website is referred to in this work as a citation and/or a potential source of further information does not mean that the author or the publisher endorses the information the organization or website may provide or recommendations it may make. Further, readers should be aware that internet websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the publisher nor the author shall be liable for any damages arising herefrom.

*Library of Congress Cataloging-in-Publication Data*

Medical pharmacology at a glance / Michael J. Neal. – 7th ed.

p. ; cm. – (At a glance series)

Includes bibliographical references and index.

ISBN-13: 978-0-470-65789-8 (pbk. : alk. paper)

ISBN-10: 0-470-65789-8

I. Title. II. Series: At a glance series (Oxford, England)

[DNLM: 1. Pharmacology, Clinical. QV 38]

LC classification not assigned

615'.1–dc23

2011034157

A catalogue record for this book is available from the British Library.

Set in 9 on 11.5 pt Times by Toppan Best-set Premedia Limited

# Preface

This book is written primarily for medical students but it should also be useful to students and scientists in other disciplines who would like an elementary and concise introduction to pharmacology.

In this book the text has been reduced to a minimum for understanding the figures. Nevertheless, I have attempted in each chapter to

explain how the drugs produce their effects and to outline their uses.

In this seventh edition the chapters have been updated and a new chapter on immunosuppressants has been added.

## Acknowledgements

I am grateful to Professor J.M. Ritter, Professor M. Marbur and Professor P.J. Ciclitira for their advice and helpful comments on the case studies relevant to their special interests.

## How to use this book

Each of the chapters (listed on page 5) represents a particular topic, corresponding roughly to a 60-minute lecture. Beginners in pharmacology should start at Chapter 1 and first read through the text on the left-hand pages (which occasionally continues to the facing right-hand page above the ruled line) of several chapters, using the figures only as a guide.

Once the general outline has been grasped, it is probably better to concentrate on the *figures* one at a time. Some are quite complicated and certainly cannot be taken in 'at a glance'. Each should be studied

carefully and worked through together with the legends (right-hand pages). Because many drugs appear in more than one chapter, considerable cross-referencing has been provided. As progress is made through the book, use of this cross-referencing will provide valuable reinforcement and a greater understanding of drug action. Once the information has been understood, the figures should subsequently require little more than a brief look to refresh the memory.

The figures are highly diagrammatic and not to scale.

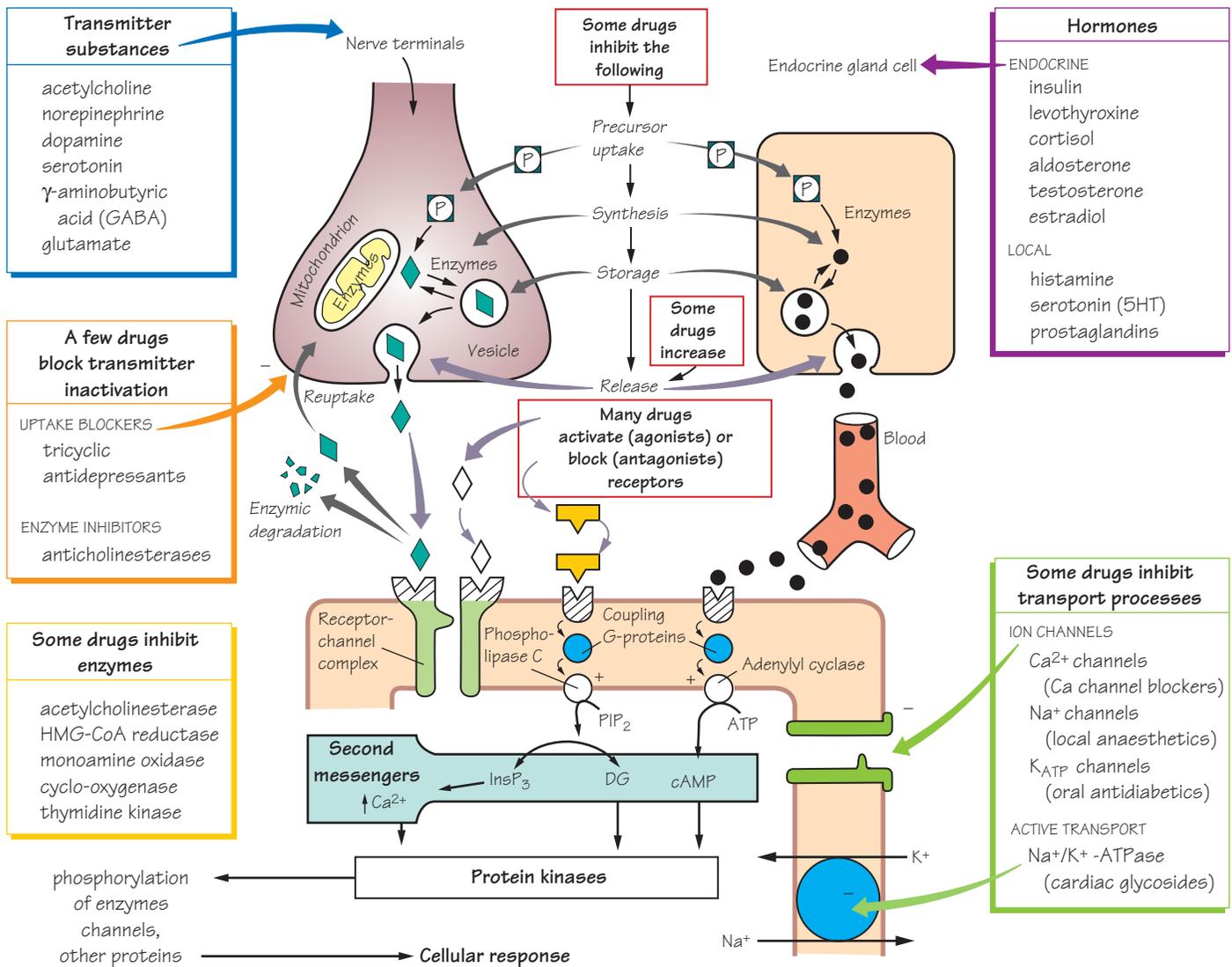
## Further reading

*British National Formulary*. British Medical Association and The Royal Pharmaceutical Society of Great Britain, London (about 1000 pp). The BNF is updated twice a year.

Rang, H.P., Dale, M.M., Ritter, J.M., Flower, R.J. & Henderson, G. (2011) *Pharmacology*, 7th edn, Churchill Livingstone, Edinburgh (829 pp).

Bennett, P.N. & Brown, M.J. (2008) *Clinical Pharmacology*, 10th edn, Churchill Livingstone, Edinburgh (694 pp).

# 1 Introduction: principles of drug action



Medical pharmacology is the science of chemicals (drugs) that interact with the human body. These interactions are divided into two classes:

- **pharmacodynamics** – the effects of the drug on the body; and
- **pharmacokinetics** – the way the body affects the drug with time (i.e. absorption, distribution, metabolism and excretion).

The most common ways in which a drug can produce its effects are shown in the figure. A few drugs (e.g. activated charcoal, osmotic diuretics) act by virtue of their physicochemical properties, and this is called **non-specific** drug action. Some drugs act as false substrates or inhibitors for certain **transport systems** (bottom right) or **enzymes** (bottom left). However, most drugs produce their effects by acting on specific protein molecules, usually located in the cell membrane. These proteins are called **receptors** (⊕), and they normally respond to endogenous chemicals in the body. These chemicals are either synaptic **transmitter substances** (top left, ◆) or **hormones** (top right, ●). For example, acetylcholine is a transmitter substance released from

motor nerve endings; it activates receptors in skeletal muscle, initiating a sequence of events that results in contraction of the muscle. Chemicals (e.g. acetylcholine) or drugs that activate receptors and produce a response are called **agonists** (◆). Some drugs, called **antagonists** (▽), combine with receptors, but do not activate them. Antagonists reduce the probability of the transmitter substance (or another agonist) combining with the receptor and so reduce or block its action.

The activation of receptors by an agonist or hormone is coupled to the physiological or biochemical responses by transduction mechanisms (lower figure) that often (but not always) involve molecules called '**second messengers**' (□).

The interaction between a drug and the binding site of the receptor depends on the complementarity of 'fit' of the two molecules. The closer the fit and the greater the number of bonds (usually noncovalent), the stronger will be the attractive forces between them, and the higher the **affinity** of the drug for the receptor. The ability of a drug

to combine with one particular type of receptor is called **specificity**. No drug is truly specific, but many have a relatively **selective** action on one type of receptor.

Drugs are prescribed to produce a therapeutic effect, but they often produce additional **unwanted effects** (Chapter 46) that range from the trivial (e.g. slight nausea) to the fatal (e.g. aplastic anaemia).

## Receptors

These are protein molecules that are normally activated by transmitters or hormones. Many receptors have now been cloned and their amino acid sequences determined. The four main types of receptor are listed below.

**1** Agonist (ligand)-gated ion channels are made up of protein subunits that form a central pore (e.g. nicotinic receptor, Chapter 6;  $\gamma$ -aminobutyric acid (GABA) receptor, Chapter 24).

**2** G-protein-coupled receptors (see below) form a family of receptors with seven membrane-spanning helices. They are linked (usually) to physiological responses by second messengers.

**3** Nuclear receptors for steroid hormones (Chapter 34) and thyroid hormones (Chapter 35) are present in the cell nucleus and regulate transcription and thus protein synthesis.

**4** Kinase-linked receptors are surface receptors that possess (usually) intrinsic tyrosine kinase activity. They include receptors for insulin, cytokines and growth factors (Chapter 36).

**Transmitter substances** are chemicals released from nerve terminals that diffuse across the synaptic cleft and bind to the receptors. This binding activates the receptors by changing their conformation, and triggers a sequence of postsynaptic events resulting in, for example, muscle contraction or glandular secretion. Following its release, the transmitter is inactivated (left of figure) by either enzymic degradation (e.g. acetylcholine) or reuptake (e.g. norepinephrine [noradrenaline], GABA). Many drugs act by either reducing or enhancing synaptic transmission.

**Hormones** are chemicals released into the bloodstream; they produce their physiological effects on tissues possessing the necessary specific hormone receptors. Drugs may interact with the endocrine system by inhibiting (e.g. antithyroid drugs, Chapter 35) or increasing (e.g. oral antidiabetic agents, Chapter 36) hormone release. Other drugs interact with hormone receptors, which may be activated (e.g. steroidal anti-inflammatory drugs, Chapter 33) or blocked (e.g. oestrogen anti-gonists, Chapter 34). Local hormones (autacoids), such as histamine, serotonin (5-hydroxytryptamine, 5HT), kinins and prostaglandins, are released in pathological processes. The effects of histamine can sometimes be blocked with antihistamines (Chapter 11), and drugs that block prostaglandin synthesis (e.g. aspirin) are widely used as anti-inflammatory agents (Chapter 32).

## Transport systems

The lipid cell membrane provides a barrier against the transport of hydrophilic molecules into or out of the cell.

**Ion channels** are selective pores in the membrane that allow the ready transfer of ions down their electrochemical gradient. The open-closed state of these channels is controlled either by the membrane potential (voltage-gated channels) or by transmitter substances (ligand-gated channels). Some channels (e.g.  $\text{Ca}^{2+}$  channels in the heart) are both voltage and transmitter gated. Voltage-gated channels for sodium, potassium and calcium have the same basic structure (Chapter 5), and subtypes exist for each different channel. Important examples of drugs that act on voltage-gated channels are *calcium-channel block-*

*ers* (Chapter 16), which block L-type calcium channels in vascular smooth muscle and the heart, and *local anaesthetics* (Chapter 5), which block sodium channels in nerves. Some *anticonvulsants* (Chapter 25) and some *antiarrhythmic* drugs (Chapter 17) also block  $\text{Na}^+$  channels. No clinically useful drug acts primarily on voltage-gated  $\text{K}^+$  channels, but *oral antidiabetic* drugs act on a different type of  $\text{K}^+$  channel that is regulated by intracellular adenosine triphosphate (ATP, Chapter 36).

**Active transport processes** are used to transfer substances against their concentration gradients. They utilize special carrier molecules in the membrane and require metabolic energy. Two examples are listed below.

**1** *Sodium pump*. This expels  $\text{Na}^+$  ions from inside the cell by a mechanism that derives energy from ATP and involves the enzyme adenosine triphosphatase (ATPase). The carrier is linked to the transfer of  $\text{K}^+$  ions into the cell. The *cardiac glycosides* (Chapter 18) act by inhibiting the  $\text{Na}^+/\text{K}^+$ -ATPase.  $\text{Na}^+$  and/or  $\text{Cl}^-$  transport processes in the kidney are inhibited by some *diuretics* (Chapter 14).

**2** *Norepinephrine transport*. The *tricyclic antidepressants* (Chapter 28) prolong the action of norepinephrine by blocking its reuptake into central nerve terminals.

## Enzymes

These are catalytic proteins that increase the *rate* of chemical reactions in the body. Drugs that act by inhibiting enzymes include: *anticholinesterases*, which enhance the action of acetylcholine (Chapters 6 and 8); *carbonic anhydrase inhibitors*, which are diuretics (i.e. increase urine flow, Chapter 14); *monoamine oxidase inhibitors*, which are antidepressants (Chapter 28); and inhibitors of *cyclo-oxygenase* (e.g. aspirin, Chapter 32).

## Second messengers

These are chemicals whose intracellular concentration increases or, more rarely, decreases in response to receptor activation by agonists, and which trigger processes that eventually result in a cellular response. The most studied second messengers are:  $\text{Ca}^{2+}$  ions, cyclic adenosine monophosphate (cAMP), inositol-1,4,5-trisphosphate ( $\text{InsP}_3$ ) and diacylglycerol (DG).

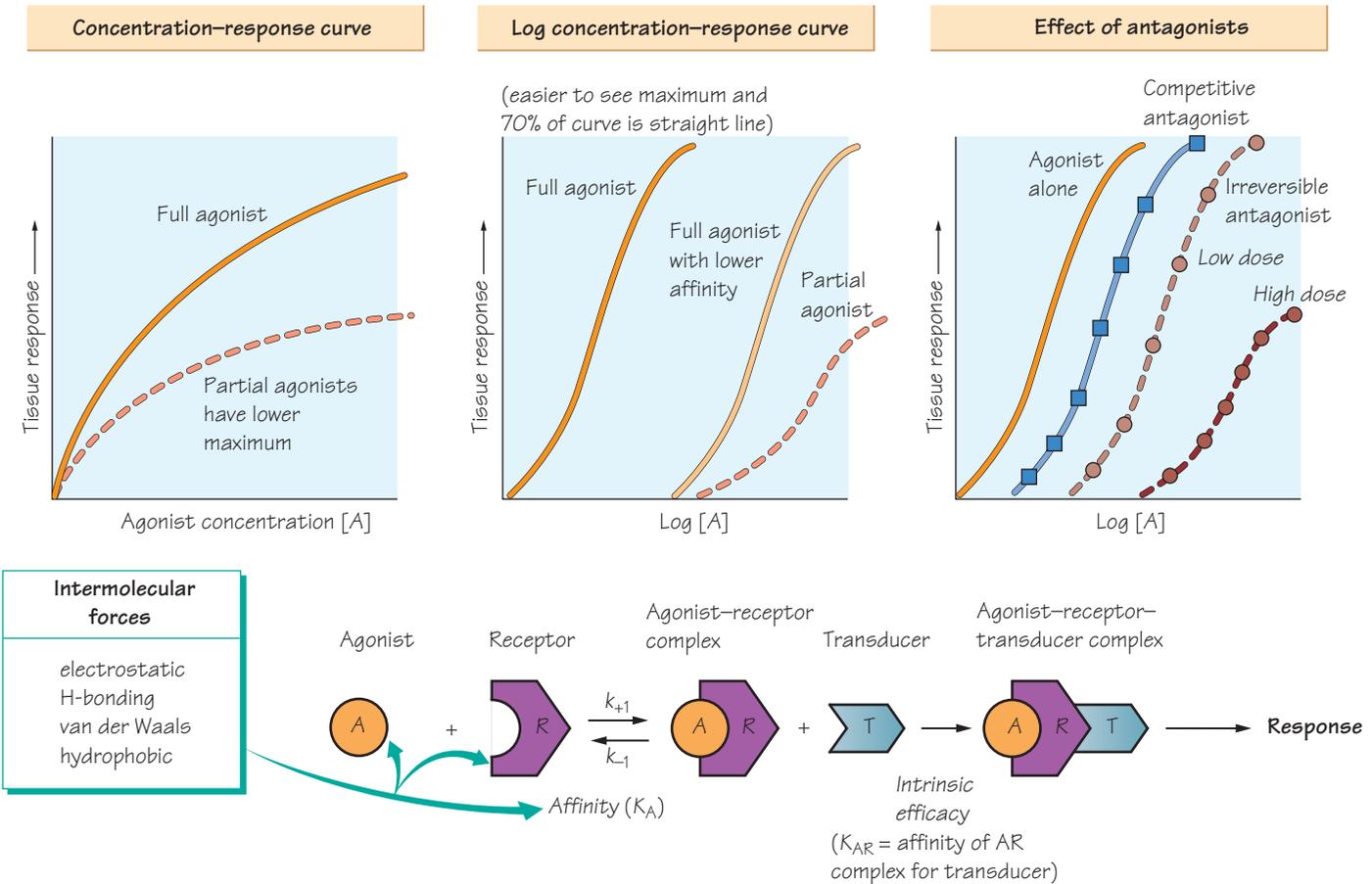
cAMP is formed from ATP by the enzyme adenylyl cyclase when, for example,  $\beta$ -adrenoceptors are stimulated. The cAMP activates an enzyme (protein kinase A), which phosphorylates a protein (enzyme or ion channel) and leads to a physiological effect.

$\text{InsP}_3$  and DG are formed from membrane phosphatidylinositol 4,5-bisphosphate by activation of a phospholipase C. Both messengers can, like cAMP, activate kinases, but  $\text{InsP}_3$  does this indirectly by mobilizing intracellular calcium stores. Some muscarinic effects of acetylcholine and  $\alpha_1$ -adrenergic effects involve this mechanism (Chapter 7).

## G-proteins

G-protein-coupled receptors are linked to their responses by a family of regulatory guanosine triphosphate (GTP)-binding proteins (G-proteins). The receptor-agonist complex induces a conformational change in the G-protein, causing its  $\alpha$ -subunit to bind GTP. The  $\alpha$ -GTP complex dissociates from the G-protein and activates (or inhibits) the membrane enzyme or channel. The signal to the enzyme or channel ends because  $\alpha$ -GTP has intrinsic GTPase activity and turns itself off by hydrolysing the GTP to guanosine diphosphate (GDP).  $\alpha$ -GDP then reassociates with the  $\beta\gamma$  G-protein subunits.

## 2 Drug–receptor interactions



The tissues in the body have only a few basic responses when exposed to agonists (e.g. muscle contraction, glandular secretion), and the quantitative relationship between these physiological responses and the concentration of the agonist can be measured by using **bioassays**. The first part of the drug–receptor interaction, i.e. the **binding of drug to receptor**, can be studied in isolation using **binding assays**.

It has been found by experiment that, for many tissues and agonists, when the response is plotted against the concentration of the drug, a curve is produced that is often hyperbolic (**concentration–response curve**, top left). In practice, it is often more convenient to plot the response against the logarithm of the agonist concentration (**log concentration–response curve**, middle top). Assuming that the interaction between the drug (*A*) and the receptor (*R*) (lower figure) obeys the law of mass action, then the concentration of the drug–receptor complex (*AR*) is given by:

$$[AR] = \frac{[R_0][A]}{K_D + [A]}$$

where  $R_0$  = total concentration of receptors,  $A$  = agonist concentration,  $K_D$  = dissociation constant and  $AR$  = concentration of occupied receptors.

As this is the equation for a hyperbola, the shape of the dose–response curve is explained if the response is directly proportional to  $[AR]$ . Unfortunately, this simple theory does not explain another experimental finding – some agonists, called **partial agonists**, cannot

elicit the same maximum response as full agonists even if they have the same affinity for the receptor (top left and middle, — —). Thus, in addition to having affinity for the receptor, an agonist has another chemical property, called **intrinsic efficacy**, which is its ability to elicit a response when it binds to a receptor (lower figure).

A **competitive antagonist** has no intrinsic efficacy and, by occupying a proportion of the receptors, effectively dilutes the receptor concentration. This causes a parallel shift of the log concentration–response curve to the right (top right, ■), but the maximum response is not depressed. In contrast, **irreversible antagonists** depress the maximum response (top right, ●). However, at low concentrations, a parallel shift of the log concentration–response curve may occur without a reduction in the maximum response (top right, ●). Because an irreversible antagonist in effect removes receptors from the system, it is clear that not all of the receptors need to be occupied to elicit the maximum response (i.e. there is a **receptor reserve**).

### Binding of drugs to receptors

#### Intermolecular forces

Drug molecules in the environment of receptors are attracted initially by relatively long-range electrostatic forces. Then, if the molecule is suitably shaped to fit closely to the binding site of the receptor, hydrogen bonds and van der Waals forces briefly bind the drug to the receptor. Irreversible antagonists bind to receptors with strong covalent bonds.

## Affinity

This is a measure of how avidly a drug binds to its receptor. It is characterized by the equilibrium dissociation constant ( $K_D$ ), which is the ratio of rate constants for the reverse ( $k_{-1}$ ) and forward ( $k_{+1}$ ) reactions between the drug and the receptor. The reciprocal of  $K_D$  is called the affinity constant ( $K_A$ ), and (in the absence of receptor reserve, see below) is the concentration of drug that produces 50% of the maximum response.

## Antagonists

Most antagonists are drugs that *bind to receptors but do not activate them*. They may be competitive or irreversible. Other types of antagonist are less common.

**Competitive antagonists** bind reversibly with receptors, and the tissue response can be returned to normal by increasing the dose of agonist, because this increases the probability of agonist–receptor collisions at the expense of antagonist–receptor collisions. The ability of higher doses of agonist to overcome the effects of the antagonist results in a parallel shift of the dose–response curve to the right and is the hallmark of competitive antagonism.

**Irreversible antagonists** have an effect that cannot be reversed by increasing the concentration of agonist. The only important example is *phenoxybenzamine*, which binds covalently with  $\alpha$ -adrenoceptors. The resulting insurmountable block is valuable in the management of phaeochromocytoma, a tumour that releases large amounts of epinephrine (adrenaline).

## Other types of antagonism

**Non-competitive antagonists** do not bind to the receptor site but act downstream to prevent the response to an agonist, e.g. calcium-channel blockers (Chapter 15).

**Chemical antagonists** simply bind to the active drug and inactivate it; e.g. protamine abolishes the anticoagulant effect of heparin (Chapter 19).

**Physiological antagonists** are two agents with opposite effects that tend to cancel one another out, e.g. prostacyclin and thromboxane  $A_2$  on platelet aggregation (Chapter 19).

## Receptor reserve

In some tissues (e.g. smooth muscle), irreversible antagonists initially shift the log dose–response curve to the right without reducing the maximum response, indicating that the maximum response can be obtained without the agonist occupying all the receptors. The excess receptors are sometimes called ‘spare’ receptors, but this is a misleading term because they are of functional significance. They increase both the sensitivity and speed of a system because the concentration of drug–receptor complex (and hence the response) depends on the product of the agonist concentration and the *total* receptor concentration.

## Partial agonists

These are agonists that cannot elicit the same maximum response as a ‘full’ agonist. The reasons for this are unknown. One suggestion is that agonism depends on the affinity of the drug–receptor complex for a *transducer molecule* (lower figure). Thus, a full agonist produces a complex with high affinity for the transducer (e.g. the coupling G-proteins, Chapter 1), whereas a partial agonist–receptor complex has a lower affinity for the transducer and so cannot elicit the full response.

When acting alone at receptors, partial agonists stimulate a physiological response, but they can antagonize the effects of a full agonist.

This is because some of the receptors previously occupied by the full agonist become occupied by the partial agonist, which has a smaller effect (e.g. some  $\beta$ -adrenoceptor antagonists, Chapters 15 and 16).

## Intrinsic efficacy

This is the ability of an agonist to alter the conformation of a receptor in such a way that it elicits a response in the system. It is defined as the affinity of the agonist–receptor complex for a transducer.

**Partial agonists and receptor reserve.** A drug that is a partial agonist in a tissue with no receptor reserve may be a full agonist in a tissue possessing many ‘spare’ receptors, because its poor efficacy can be offset by activating a larger number of receptors than that required by a full agonist.

## Bioassay

Bioassays involve the use of a biological tissue to relate drug concentration to a physiological response. Usually isolated tissues are used because it is then easier to control the drug concentration around the tissue and reflex responses are abolished. However, bioassays sometimes involve whole animals, and the same principles are used in clinical trials.

Bioassays can be used to estimate:

- the concentration of a drug (largely superseded by chemical methods);
- its binding constants; or
- its potency relative to another drug.

Measurement of the relative potencies of a series of agonists on different tissues has been one of the main ways used to classify receptors, e.g. adrenoceptors (Chapter 7).

## Binding assays

Binding assays are simple and very adaptable. Membrane fragments from homogenized tissues are incubated with radiolabelled drug (usually  $^3\text{H}$ ) and then recovered by filtration. After correction for non-specific binding, the [ $^3\text{H}$ ]drug bound to the receptors can be determined and estimations made of  $K_A$  and  $B_{\text{max}}$  (number of binding sites). Binding assays are widely used to study drug receptors, but have the disadvantage that no functional response is measured, and often the radiolabelled drug does not bind to a single class of receptor.

## Localization of receptors

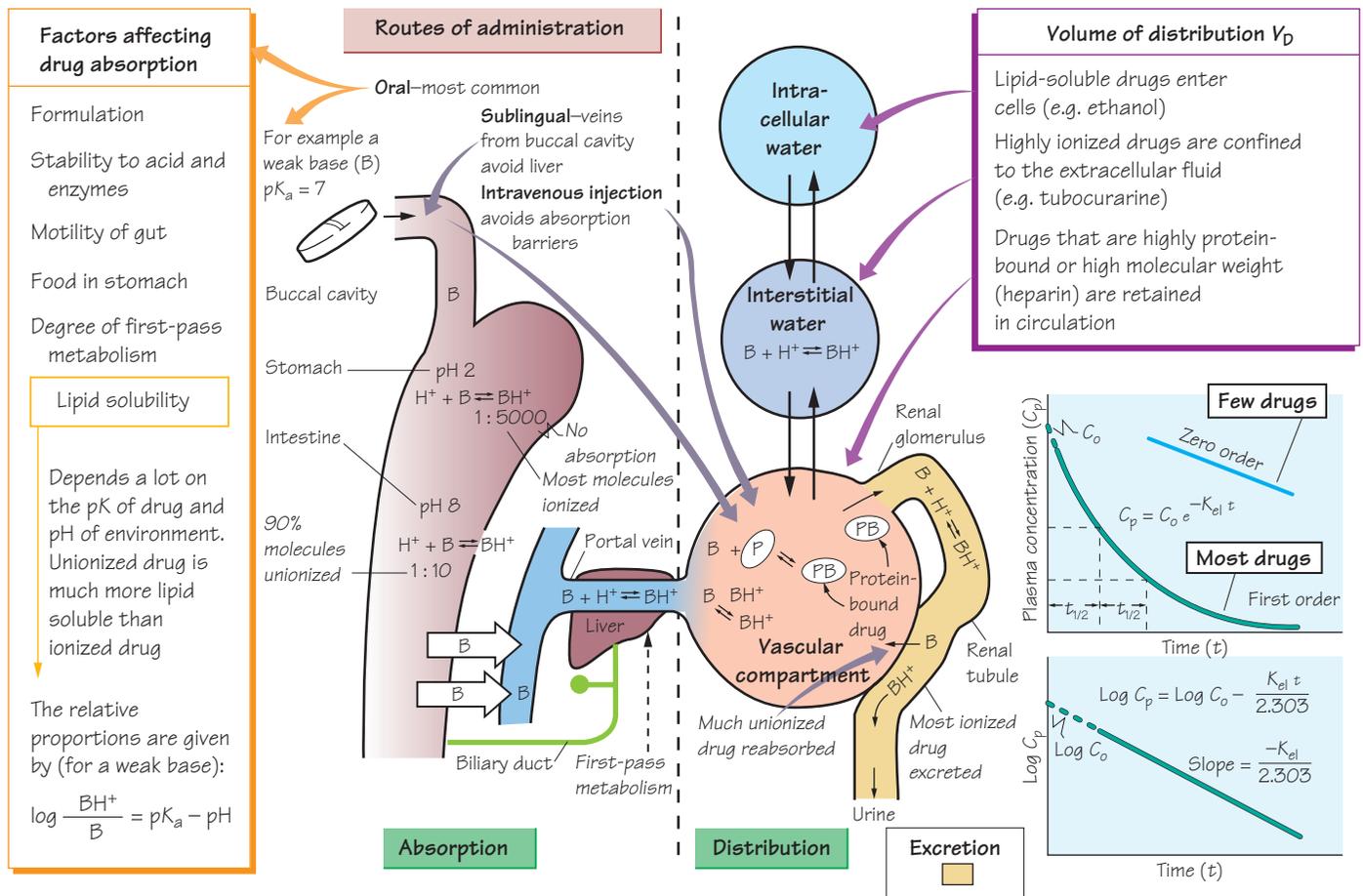
The distribution of receptors, e.g. in sections of the brain, can be studied using autoradiography. In humans, positron-emitting drugs can sometimes be used to obtain images (positron emission tomography [PET] scanning) showing the location and density of receptors, e.g. dopamine receptors in the brain (Chapter 27).

## Tachyphylaxis, desensitization, tolerance and drug resistance

When a drug is given repeatedly, its effects often decrease with time. If the decrease in effect occurs quickly (minutes), it is called **tachyphylaxis** or desensitization. **Tolerance** refers to a slower decrease in response (days or weeks). **Drug resistance** is a term reserved for the loss of effect of chemotherapeutic agents, e.g. antimalarials (Chapter 43). Tolerance may involve increased metabolism of a drug, e.g. ethanol, barbiturates (Chapter 3), or homeostatic mechanisms (usually not understood) that gradually reduce the effect of a drug, e.g. morphine (Chapter 29). Changes in receptors may cause desensitization, e.g. suxamethonium (Chapter 6). A decrease in receptor number (downregulation) can lead to tolerance, e.g. insulin (Chapter 36).

## 3

## Drug absorption, distribution and excretion



Most drugs are given **orally** and they must pass through the gut wall to enter the bloodstream (left of figure,  $\Rightarrow$ ). This **absorption** process is affected by many factors (left), but is usually proportional to the **lipid solubility** of the drug. Thus, the absorption of non-ionized molecules (B) is favoured because the latter are far more lipid soluble than ionized molecules ( $BH^+$ ), which are surrounded by a 'shell' of water molecules. Drugs are absorbed mainly from the small intestine because of the latter's large surface area. This is true even for weak acids (e.g. aspirin), which are non-ionized in the acid (HCl) of the stomach. Drugs absorbed from the gastrointestinal tract enter the portal circulation (left,  $\square$ ) and some are extensively metabolized as they pass through the liver (first-pass metabolism).

Drugs that are sufficiently lipid soluble to be readily absorbed orally are rapidly distributed throughout the body water compartments (○). Many drugs are loosely bound to plasma albumin, and an equilibrium forms between the bound (PB) and free (B) drug in the plasma. Drug that is bound to plasma proteins is confined to the vascular system and cannot exert its pharmacological actions.

If a drug is given by **intravenous injection**, it enters the blood and is rapidly distributed to the tissues. By taking repeated blood

samples, the fall in plasma concentration of the drug with time (i.e. the rate of drug elimination) can be measured (right, top graph). Often the concentration falls rapidly at first, but then the rate of decline progressively decreases. Such a curve is called **exponential**, and this means that, at any given time, a **constant fraction** of the drug present is eliminated in unit time. Many drugs show an exponential fall in plasma concentration because the rates at which the drug elimination processes work are themselves usually proportional to the concentration of drug in the plasma. The following processes are involved.

- 1 Elimination in the urine by glomerular filtration (right,  $\square$ ).
- 2 Metabolism, usually by the liver.
- 3 Uptake by the liver and subsequent elimination in the bile ( $\text{—}$  solid line from liver).

A process that depends on the concentration at any given time is called **first order**; most drugs exhibit first-order elimination kinetics. If any enzyme system responsible for drug metabolism becomes **saturated**, then the elimination kinetics change to **zero order**, i.e. the rate of elimination proceeds at a constant rate and is unaffected by an increased concentration of the drug (e.g. ethanol, phenytoin).

## Routes of administration

Drugs can be administered orally or parenterally (i.e. by a nongastrointestinal route).

**Oral** Most drugs are absorbed by this route and, because of its convenience, it is the most widely used. However, some drugs (e.g. benzylpenicillin, insulin) are destroyed by the acid or enzymes in the gut and must be given parenterally.

**Intravenous injection** The drug directly enters into the circulation and bypasses the absorption barriers. It is used:

- where a rapid effect is required (e.g. furosemide in pulmonary oedema);
- for continuous administration (infusion);
- for large volumes; and
- for drugs that cause local tissue damage if given by other routes (e.g. cytotoxic drugs).

**Intramuscular and subcutaneous injections** Drugs in aqueous solution are usually absorbed fairly rapidly, but absorption can be slowed by giving the drug in the form of an ester (e.g. antipsychotic depot preparations, Chapter 27).

**Other routes** These include **inhalation** (e.g. volatile anaesthetics, some drugs used in asthma) and **topical** (e.g. ointments). **Sublingual** and **rectal** administration avoids the portal circulation, and sublingual preparations in particular are valuable in administering drugs subject to a high degree of first-pass metabolism.

## Distribution and excretion

Distribution around the body occurs when the drug reaches the circulation. It must then penetrate tissues to act.

The  $t_{1/2}$  (**half-life**) is the time taken for the concentration of drug in the blood to fall by half its original value (right, top graph). Measurement of  $t_{1/2}$  allows the calculation of the *elimination rate constant* ( $K_{el}$ ) from the formula:

$$K_{el} = \frac{0.69}{t}$$

where  $K_{el}$  is the fraction of drug present at any time that would be eliminated in unit time (e.g.  $K_{el} = 0.02 \text{ min}^{-1}$  means that 2% of the drug present is eliminated in 1 min).

The exponential curve of plasma concentration ( $C_p$ ) against time ( $t$ ) is described by:

$$C_p = C_0 e^{-K_{el}t}$$

where  $C_0$  = the initial apparent plasma concentration. By taking logarithms, the exponential curve can be transformed into a more convenient straight line (right, bottom graph) from which  $C_0$  and  $t_{1/2}$  can readily be determined.

**Volume of distribution ( $V_D$ )** This is the apparent volume into which the drug is distributed. Following an intravenous injection:

$$V_D = \frac{\text{dose}}{C_0}$$

A value of  $V_D < 5 \text{ L}$  implies that the drug is retained within the vascular compartment. A value of  $< 15 \text{ L}$  suggests that the drug is restricted to

the extracellular fluid, whereas large volumes of distribution ( $V_D > 15 \text{ L}$ ) indicate distribution throughout the total body water or concentration in certain tissues. The volume of distribution can be used to calculate the *clearance* of the drug.

**Clearance** This is an important concept in pharmacokinetics. It is the volume of blood or plasma cleared of drug in unit time. Plasma clearance ( $Cl_p$ ) is given by the relationship:

$$Cl_p = V_D K_{el}$$

The rate of elimination =  $Cl_p \times C_p$ . Clearance is the sum of individual clearance values. Thus,  $Cl_p = Cl_m$  (metabolic clearance) +  $Cl_r$  (renal excretion). Clearance, but not  $t_{1/2}$ , provides an indication of the ability of the liver and kidney to dispose of drugs.

**Drug dosage** Clearance values can be used to plan dosage regimens. Ideally, in drug treatment, a steady-state plasma concentration ( $C_{\text{pss}}$ ) is required within a known therapeutic range. A steady state will be achieved when the rate of drug entering the systemic circulation (dosage rate) equals the rate of elimination. Thus, the dosing rate =  $Cl \times C_{\text{pss}}$ . This equation could be applied to an intravenous infusion because the entire dose enters the circulation at a known rate. For oral administration, the equation becomes:

$$\frac{F \times \text{dose}}{\text{dosing interval}} = Cl_p \times C_p, \text{ average}$$

where  $F$  = *bioavailability* of the drug. The  $t_{1/2}$  value of a drug is useful in choosing a dosing interval that does not produce excessively high peaks (toxic levels) and low troughs (ineffective levels) in drug concentration.

**Bioavailability** This is a term used to describe the proportion of administered drug reaching the systemic circulation. Bioavailability is 100% following an intravenous injection ( $F = 1$ ), but drugs are usually given orally, and the proportion of the dose reaching the systemic circulation varies with different drugs and also from patient to patient. Drugs subject to a high degree of first-pass metabolism may be almost inactive orally (e.g. glyceryl trinitrate, lidocaine).

## Excretion

**Renal excretion** This is ultimately responsible for the elimination of most drugs. Drugs appear in the glomerular filtrate, but if they are lipid soluble they are readily reabsorbed in the renal tubules by passive diffusion. Metabolism of a drug often results in a less lipid-soluble compound, aiding renal excretion (see Chapter 4).

The ionization of weak acids and bases depends on the pH of the tubular fluid. Manipulation of the urine pH is sometimes useful in increasing renal excretion. For example, bicarbonate administration makes the urine alkaline; this ionizes aspirin, making it less lipid soluble and increasing its rate of excretion.

Weak acids and weak bases are actively secreted in the proximal tubule, eg penicillins, thiazide diuretics, morphine.

**Biliary excretion** Some drugs (e.g. diethylstilbestrol) are concentrated in the bile and excreted into the intestine where they may be reabsorbed. This enterohepatic circulation increases the persistence of a drug in the body.