The Hitchhiker's Guide to Clinical Pharmacology

Pharmacodynamics: How Drugs Work

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Pharmacokinetics is about how drugs move around the body, being absorbed, distributed to their sites of action, and being eliminated. Pharmacodynamics is about all those matters that are concerned with the pharmacological actions of drugs when they get to their sites of action, whether they be determinants of beneficial or adverse effects.

1. The types of pharmacological actions of drugs

The different ways in which drugs produce their pharmacological effects are classified in Table 1. Several of the examples I shall illustrate cross the boundaries of this classification. For example, cardiac glycosides can be considered as ligands that act by binding to their receptor (the Na/K-ATPase), as inhibitors of an enzyme (the Na/K-ATPase), or as inhibitors of a transport process (the Na/K pump). This reflects the complexities of pharmacology.

Table 1. The types of pharmacological actions of drugs

1. Drug action via a receptor
   (a) Agonists
   (b) Antagonists
   (c) Partial agonists
   (d) Inverse agonists
2. Drug action via indirect alteration of the effect of an endogenous agonist
   (a) Physiological antagonism
   (b) Increase in endogenous release
   (c) Inhibition of endogenous re-uptake
   (d) Inhibition of endogenous metabolism
   (e) Prevention of endogenous release
3. Drug action via the inhibition of transport processes
4. Drug action via enzyme inhibition
5. Drug action via enzymatic action or activation of enzyme activity
6. Drug action via other miscellaneous effects
   (a) Chelating agents
   (b) Osmotic diuretics
   (c) Volatile general anaesthetics
   (d) Replacement drugs

1.1. Drug action via a direct effect on a receptor

Receptors are specific proteins, situated either in cell membranes or, in some cases, in the cellular cytoplasm. For each type of receptor, there is a specific group of drugs or endogenous substances (known as ligands) that are capable of binding to the receptor, producing a pharmacological effect. Most receptors are located on the cell surface. However, some drugs act on intracellular receptors; these include corticosteroids, which act on cytoplasmic steroid receptors, and the thiazolidinediones (such as pioglitazone), which activate peroxisome proliferator-activated receptor gamma (PPARy), a nuclear receptor involved in the expression of genes involved in lipid metabolism and insulin sensitivity. The important receptor systems and their ligands are listed in Table 2.

There are four types of ligand that act by binding to a cell surface receptor, agonists, antagonists, partial agonists, and inverse agonists (Figure 1).

(a) Agonists

Ligand s that bind to a receptor and produce an appropriate response are called agonists. For example, the catecholamine adrenaline is an agonist at β-adrenoceptors. When it binds to β-adrenoceptors in the heart, it increases the heart rate.

(b) Antagonists

Ligands that prevent an agonist from binding to a receptor and thus prevent its effects are called antagonists. Antagonists do not themselves have any pharmacological actions mediated by receptors. For example, propranolol, a β-adrenoceptor antagonist, binds to β-adrenoceptors in the heart and prevents catecholamine-induced tachycardia (for example in response to exercise). However, in the absence of an agonist propranolol has no effect via adrenoceptors.

Table 2. Examples of important receptors, their agonists and antagonists

Receptor type	Subtype	Site(s) in the body	Agonists	Antagonists
Adrenoceptors	α/β		Adrenaline Noradrenaline	Labetalol
	α_1/α_2			Phentolamine Phenoxybenzamine
	α_1	Pupillary dilator muscle Vascular smooth muscle	Dopamine (high doses) Phenylephrine	Doxazosin Indoramin Prazosin
	α_2	CNS Presynaptic nerve terminals	Clonidine	Yohimbine
	β_1/β_2		Dopamine Isoprenaline	Propranolol Oxprenolol
	β_1	CNS Heart	Dobutamine Dopamine (moderate doses)	Atenolol Metoprolol Propranolol
	β_2	Pancreatic islets Smooth muscle (bronchiolar, vascular, uterine)	Fenoterol Rimiterol Salbutamol Terbutaline	
Angiotensin	AT_1	Cardiovascular	Angiotensin	Eprosartan Irbesartan Losartan Valsartan
Cholinoceptors	Muscarinic	Tissues innervated by parasympathetic nerves	Acetylcholine and analogues (e.g. carbachol, bethanecol)	Atropine and analogues Disopyramide Orphenadrine Pirenzepine (M_1 selective) Quinidine Tricyclic antidepressants Trihexyphenidyl
	Nicotinic	Neuromuscular junction Postganglionic cells in ganglia	Acetylcholine and some analogues (e.g. carbachol)	Aminoglycoside antibiotics Ganglion-blocking drugs Neuromuscular-blocking drugs Quinidine
Dopamine receptors	Various	CNS Renal vasculature	Apomorphine Bromocriptine Dopamine (low doses	Butyrophenones (e.g. haloperidol) Domperidone (D_2) Metoclopramide Phenothiazines (e.g. chlorpromazine) Thioxanthenes (e.g. flupenthixol)
GABA receptors	$GABA_A$-BDZ complex	CNS	GABA Benzodiazepines	Bicuculine
	$GABA_B$	CNS (presynaptic)	GABA	Baclofen

Histamine receptors	H_1	Smooth muscle (bronchiolar, vascular, gastrointestinal)	Histamine	Antihistamines (e.g. promethazine, cetirizine)
	H_2	Stomach	Histamine	Cimetidine Ranitidine Famotidine Nizatidine
5-Hydroxy-tryptamine receptors	Various	CNS Vascular smooth muscle Gastrointestinal tract	5HT	Methysergide (5HT) Sumatriptan ($5HT_{1D}$) Ketanserin ($5HT_2$) Ondansetron ($5HT_3$)
Leukotriene receptors	$CysLT_1$	Bronchial and vascular smooth muscle	Leukotrienes	Montelukast Zafirlukast
Opioid receptors	μ, δ, and κ	Biliary tract CNS Gastrointestinal tract Genitourinary tract Pupillary muscle Vascular smooth muscle	Endorphins and enkelphalins Morphine and analogues (μ agonists) Non-opioid narcotics (μ agonists, e.g. pentazocine)	Buprenorphine (κ) (partial agonist) Methylnaltrexone (δ) Nalbuphine (μ, δ, and κ) Nalmefene (μ and κ) Nalorphine (μ) Naloxone (δ and κ) Naltrexone (μ, δ, and κ)
Vasopressin receptors	V_{1A}, V_{1b}, and V_2		Vasopressin (ADH)	Conivaptan (V_{1A} and V_2) Nelivaptan (V_{1b}) Tolvaptan (V_2)

The complexity of some drugs is illustrated by the several actions of beta-adrenoceptor antagonists (beta-blockers), as shown in Table 3.

Table 3. Differences in the actions of some beta-adrenoceptor antagonists

Drug	**Cardio-selectivity (i.e. $\beta_1 > \beta_2$)**	**Partial agonist activity**	**Membrane-stabilizing activity**	**Peripheral vasodilatation**
Atenolol	+	–	–	–
Bisoprolol	+++	–	–	+
Carvedilol	–	–	++	++
Labetalol	–	–	±	++
Metoprolol	+	–	±	+
Oxprenolol	–	+	+	–
Practolol	++	+	–	–
Propranolol	–	–	++	±
Sotalol	–	–	–	–
Timolol	–	±	±	+

+ the drug has the indicated property
– the drug does not have the indicated property
± it is not clear whether the drug does or does not have the indicated property

(c) Partial agonists

A full agonist is one that is capable of producing a maximal response, when it binds to a sufficient number of receptors. In contrast, a partial agonist cannot produce the maximal response of which the tissue is capable, even when it binds to the same number of receptors as a full agonist binds to when it produces a complete response. Since the effects of a ligand are generally produced by concentrations of the ligand that are well below those that would bind to all the receptors necessary to produce a complete response, this means that above a certain level of binding, a partial agonist may bind to receptors without producing any further increase in effect. However, in so doing, it may prevent the action of other agonists, and may thus appear to be acting as an antagonist. It is this mixture of actions that is called partial agonism. For example, oxprenolol, which is a β-adrenoceptor antagonist, is also a partial agonist. Thus, it may have less of an effect in slowing the heart rate than adrenoceptor antagonists that do not have partial agonist action (i.e. full antagonists); this partial agonism of β-blockers is sometimes called "intrinsic sympathomimetic activity" (ISA).

In the case of β-adrenoceptor antagonists, the amount of β-blockade produced by a given dose of the β-blocker will vary according to how much endogenous sympathetic nervous system activity there is: the more activity, the more β-blockade will result from the action of a partial agonist. This is clearly seen in the actions of the β-adrenoceptor agonist/antagonist xamoterol. Xamoterol acts as a β-adrenoceptor agonist in patients with mild heart failure, improving cardiac contraction. However, it acts as a β-blocker in patients with even moderate heart failure, worsening it. For this reason it has not proved useful in clinical practice.

Most receptors have subtypes, for which certain ligands have some degree of selectivity. For example, there are two main sub- types of β-adrenoceptors, called β_1 and β_2, both of which can respond to adrenaline. Some β-adrenoceptor antagonists act at both β_1 and β_2 subtypes, while some are selective for one or other subtype. For example, propranolol is an antagonist at both β_1 and β_2 receptors, while atenolol is relatively selective for β_1 receptors. Note that selectivity of this kind is only relative; while a drug such as atenolol acts primarily on β_1 receptors, at high enough concentrations it can also have effects on β_2 receptors.

(d) Inverse agonists

An inverse agonist is a compound that binds to a receptor and produces a pharmacological response that is opposite to that of the corresponding agonist. An agonist increases the activity mediated by a receptor, an inverse agonist reduces it. In the presence of the agonist the inverse agonist acts as an antagonist. An ordinary antagonist can inhibit the actions of both agonists and inverse agonists.

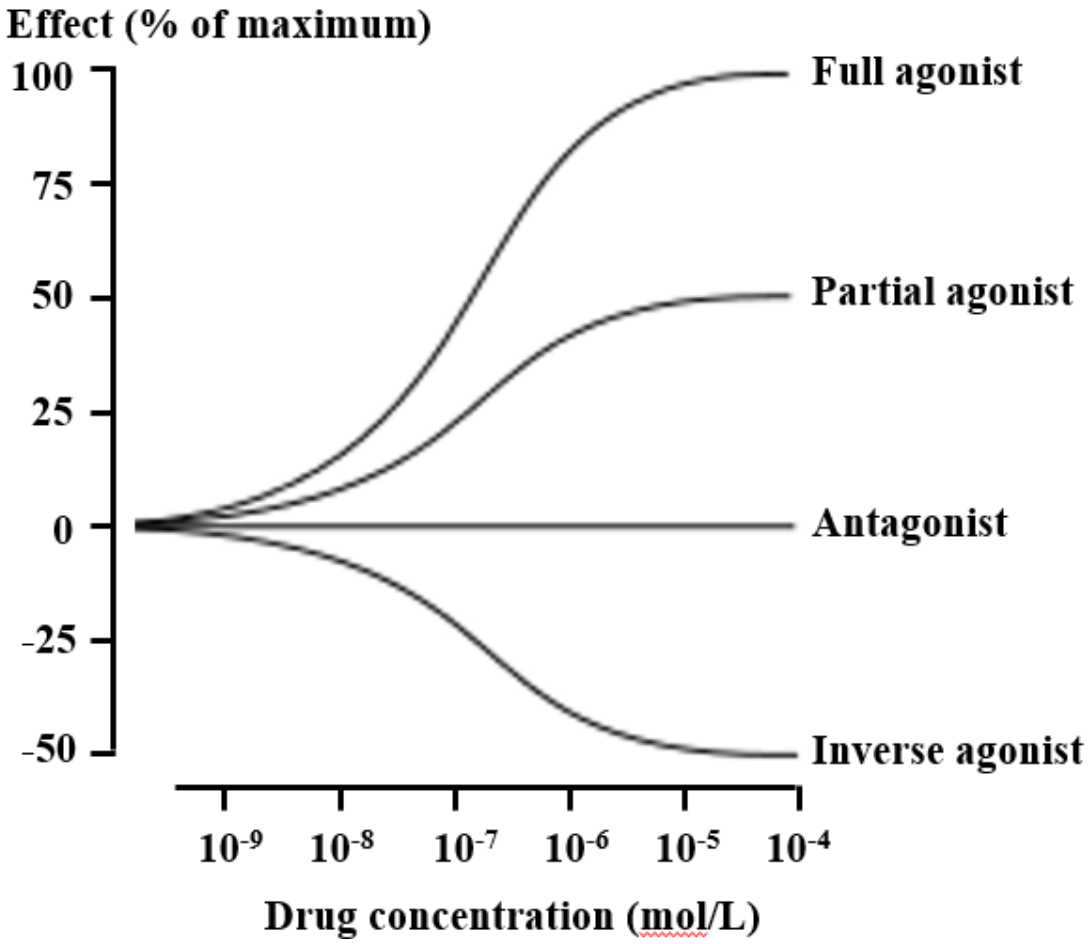

Figure 1. Theoretical dose-response curves for different types of actions of drugs at receptors

1.2 Short-term and long-term effects of drugs at receptors

Drugs and endogenous substances have two types of pharmacological effects: short-term and long-term effects.

(a) Short-term effects

Many drugs are used for their short-term effects. For example, dopamine is used as a renal arteriolar vasodilator, diamorphine to relieve pain in the treatment of myocardial ischaemia, and nebulized salbutamol to reverse bronchoconstriction in the treatment of acute severe asthma. The receptors that are involved in the action of a range of receptors are listed in Table 4.

Table 4. Transduction systems for a range of receptors

Receptor	**Transduction**
5-hydroxytryptamine (all except $5HT_3$)	$G_{i/o}$ ($5HT_{1A/1B/1D/1E/1F/5A}$); $G_{q/11}$ ($5HT_{1C/2A/2B/1E/1F}$) ; $G_{q/11}$ ($5HT_{4/6}$)
$5HT_3$	Ionotropic (cationic Cys-loop)
Acetylcholine (muscarinic)	$G_{q/11}$ ($M_{1/3/5}$); $G_{i/o}$ ($M_{2/4}$)
Acetylcholine (nicotinic)	Ionotropic (cationic Cys-loop)

Adenosine	$G_{i/o}$ ($A_{1/3}$); G_s ($A_{2A/2B}$)
Adrenoceptors (α_1)	$G_{q/11}$
Adrenoceptors (α_2)	$G_{i/o}$
Adrenoceptors (β)	G_s
Angiotensin	$G_{q/11}$ (AT_1); catalytic (tyrosine, serine, and threonine phosphatases; AT_2)
Bradykinin	$G_{q/11}$
Calcitonin	G_s and G_q
Cannabinoid	$G_{i/o}$
Chemokines	$G_{i/o}$
Cholecystokinin	$G_{q/11}$ and G_s (CCK_1); G_s (CCK_2)
Corticosteroid (glucocorticoid and mineralocorticoid)	Nuclear
Corticotropin-releasing factor	G_s
Dopamine	$G_{i/o}$ ($D_{2/3/4}$); G_s, and G_{olf} (D_1)
Endothelin	$G_{q/11}$ and G_s (ET_A); $G_{q/11}$ and $G_{i/o}$ (ET_B)
Estrogen	Nuclear; G_s (GPE)
$GABA_A$	Ionotropic (anionic Cys-loop)
$GABA_B$	$G_{i/o}$
Glucagon	G_s
Glutamate	$G_{q/11}$ ($mGlu_{1/5}$); Gi/o ($mGlu_{2/3/4/6/7/8}$); ionotropic (subtypes AMPA, kainite, NMDA)
Glycine	Ionotropic (anionic Cys-loop)
Gonadotropin-releasing hormone	$G_{q/11}$
Histamine	$G_{q/11}$ (H_1); G_s (H_2); $G_{i/o}$ ($H_{3/4}$)
Insulin	Catalytic (tyrosine kinase)
Melatonin	$G_{i/o}$
Motilin	$G_{q/11}$
Natriuretic peptides	Catalytic (guanylyl cyclase)
Opioid	$G_{i/o}$
Oxytocin	$G_{q/11}$ and $G_{i/o}$
Parathyroid hormone	G_s and $G_{q/11}$
Peroxisome proliferator activated	Nuclear
Prolactin	Catalytic (tyrosine kinase)
Prostanoid	G_s (DP_1, IP); $G_{i/o}$ (DP_2); $G_{q/11}$ (FP, TP)
Testosterone	Nuclear
Thyroid hormone	Nuclear
Toll-like	Catalytic (protein kinases)
Tumour necrosis factor	Catalytic (various)
Vasopressin	$G_{q/11}$ ($V_{1A/1B}$); G_s (V_2)
Vitamin D	Nuclear

i. Metabotropic receptors

Many agonist drugs acting on cell surface receptors known as G protein-coupled receptors (GPCRs; also called metabotropic receptors), and exert their effects through so-called second messenger systems. When a ligand binds to a GPCR a conformational change occurs, which allows the receptor to act as a guanine nucleotide exchange factor (GEF). It then activates an associated G protein by exchanging its bound GDP for a GTP. The α subunit of the G protein, together with the bound GTP, then dissociates from the β and γ subunits and has effects of intracellular signaling proteins or target functional proteins directly depending on the α subunit type. G_S and $G_{i/o}$ proteins activate adenylate cyclase and the production of cAMP; G_{q11} activates phospholipase C. The second messengers involved are shown in Figure 2 and the subtypes of G protein through which different receptors act are listed in Table 4.

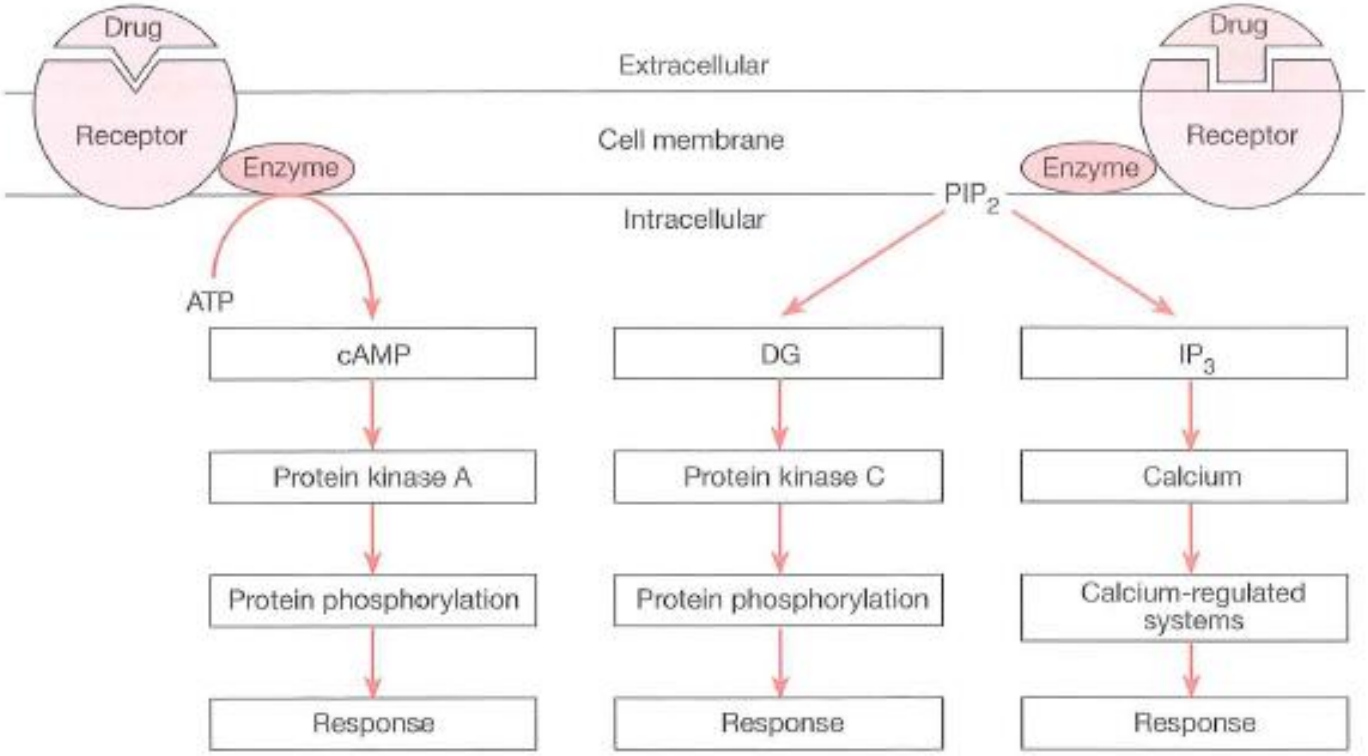

Figure 2. A schematic representation of the two types of second messenger systems that mediate the effects of drugs acting at G-protein coupled receptors. In one system (left-hand side), receptor stimulation leads to increased activity of the enzyme adenylate cyclase, which stimulates the production of cyclic AMP; this stimulates protein kinase A, which leads to protein phosphorylation and hence the response. In a second system (right-hand side), there is increased activity of the enzyme phospholipase C. In this case, stimulation of the phosphoinositide (PI) cycle leads to the response via two mechanisms, increased protein phosphorylation via stimulation of protein kinase C by diacylglycerol (DG) and activation of calcium-regulated systems in the cell.

ii. Ionotropic receptors

Ionotropic receptors mediate actions by neurotransmitters through secondary ion transport; the channels that are involved are known as ligand-gated ion channels (LGIC), which are membrane-bound proteins that contain a pore that allows selected ions to flow after the binding of the ligand. Examples (Table 4) include $GABA_A$, glycine, and some types of glutamate receptors.

iii. Nuclear receptors

Nuclear receptors are specialized intracytoplasmic transcription factors that bind to specific response elements in DNA after ligand binding and translocation to the nucleus; the response elements are in the promoter regions of specific target genes, whose transcription is thereby activated or suppressed. Examples (Table 4) include corticosteroid, testosterone, thyroid hormone, vitamin D, and peroxisome proliferator activated receptors.

iv. Catalytic receptors

Catalytic receptors are membrane-bound enzymes that have a ligand binding site and a catalytic site, which is activated or inhibited by the ligand. Examples (Table 4) include angiotensin AT_2, insulin, natriuretic peptide, prolactin, toll-like, tumour necrosis factor receptors.

(b) Long-term effects

If drugs are given for long-term therapy their short-term effects may be altered by adaptive responses that result from chronic therapy. Examples include levodopa in Parkinson's disease, β-adrenoceptor agonists in chronic asthma, and benzodiazepines in chronic anxiety. These effects are accompanied by either increases ("up-regulation") or decreases ("down-regulation") in receptor numbers during long-term therapy, and such changes can be responsible for both beneficial and adverse effects.

1.3. Soluble receptors

Some receptors can be both membrane-bound and soluble. The latter typically consist of the extracellular portions of the former. Receptors that can behave in this way include cytokine receptors (e.g. tumor necrosis factor alfa, interleukin, and interferon receptors), growth hormone receptors, and erythropoietin and thrombopoietin receptors. Some soluble receptors arise as by-products of receptor down-regulation, as receptors are downgraded. Some are produced as part of the normal function of the receptor and compete with the membrane-bound receptor for binding to the relevant ligand.

Soluble receptors can be used to prevent an endogenous ligand from binding to its membrane-bound receptor, thus reducing its cellular effects. An example is etanercept, a fusion protein that incorporates a soluble TNF-α receptor, used as a decoy receptor in the treatment of psoriasis and various types of arthropathy.

1.4. Drug action via indirect alteration of the effect of an endogenous agonist

Just as an antagonist can produce a therapeutic effect by directly opposing the action of an endogenous agonist, so the effects of an endogenous agonist can be altered in indirect ways.

(a) Physiological antagonism

A drug that produces the opposite physiological effect to that of an agonist will indirectly oppose the action of that agonist. For example, glucagon is a physiological antagonist of the actions of insulin and can be used to treat insulin-induced hypoglycaemia.

(b) Increased endogenous release

The action of an endogenous agonist is enhanced if its release is increased. For example, amphetamines increase the release of monoamines, such as dopamine, from nerve terminals.

Because amphetamines can cause a syndrome similar to schizophrenia, this action has led to the idea that schizophrenia may be related to excess dopamine action in the brain.

(c) Inhibition of endogenous re-uptake

Conversely, if a drug inhibits the reuptake of an endogenous agonist, it will enhance its effects. For example, some antidepressants, such as tricyclic antidepressants and selective serotonin reuptake inhibitors, inhibit the reuptake by neurons of neurotransmitters such as noradrenaline and 5-hydroxytryptamine.

(d) Inhibition of endogenous metabolism

If a drug inhibits the metabolism of an endogenous agonist it will enhance its effects. For example, the monoamine oxidase (MAO) inhibitors inhibit the metabolism of monoamines such as adrenaline and noradrenaline, enhancing their actions.

(e) Prevention of endogenous release

Prevention of the release of an endogenous agonist will reduce its effects. For example, one of the proposed mechanisms whereby the cromones, such as sodium cromoglicate, produce their therapeutic effects in asthma is by inhibiting the release of inflammatory mediators from mast cells in the lungs. Angiotensin-converting enzyme (ACE) inhibitors prevent the formation of angiotensin II; this reduces the endogenous release of aldosterone, whose effects on sodium and potassium excretion are thereby reduced, resulting in potassium retention.

1.5. Drug action via inhibition of transport processes

Because the transport and disposition of cations (such as sodium, potassium, and calcium) and of other substances (such as organic acids in the kidneys and neurotransmitters in the nervous system) play so many important roles in the maintenance of normal cellular functions, inhibition of their transport is an important type of mechanism of drug action. The following are examples of the ways in which drugs may act through inhibition of transport processes.

(a) Diuretics

Many diuretics act by inhibiting sodium reabsorption in the renal tubules, although they do so by different mechanisms. For example, the loop diuretics furosemide and bumetanide act at the luminal surface of the ascending limb of the loop of Henle by inhibiting the active transport system known as Na/K/Cl co-transport, which involves the transport of sodium, potassium, and chloride in the same direction across cell membranes. The potassium-sparing diuretic amiloride acts by inhibiting sodium channels in the distal segment of the distal convoluted tubule. The thiazide diuretics act by inhibiting the Na/Cl co-transport system in the proximal segment of the distal convoluted tubule. Although most of the diuretic effect of the cardiac glycosides occurs by virtue of increased cardiac output and therefore increased renal blood flow, part of its action occurs via inhibition of renal tubular Na/K-ATPase.

However, some diuretics act by mechanisms other than direct actions on transport processes. For example, spironolactone is a competitive antagonist at aldosterone receptors in the distal convoluted tubule, and acetazolamide is an enzyme inhibitor, inhibiting the action of carbonic anhydrase in the proximal convoluted tubule.

(b) Calcium channel blockers

The calcium channel blockers, such as verapamil, diltiazem, and the dihydropyridines (for example nifedipine and amlodipine), act by inhibiting the transmembrane transport of calcium through potential-operated L-type calcium channels in cell membranes. The different drugs have different specificities for calcium channels in different tissues, and because calcium plays so many important roles in these tissues, the drugs have several different actions, principal among

which are an antiarrhythmic action in the heart (for example verapamil) and a vasodilator action on peripheral arterioles (for example nifedipine). A T-type calcium channel blocker, mibefradil, which did not cause a reflex tachycardia (unlike the L-type channel blockers) was used to treat hypertension, but had to be taken off the market because it was involved in so many adverse drug-drug interactions.

(c) Insulin

One of the many actions of insulin is to increase the inward flux of glucose into cells by an action mediated via insulin receptors. In the treatment of hyperglycaemia in diabetes, the rapid fall in blood glucose produced by insulin is undoubtedly due to this action. Insulin also causes an inward flux of potassium into cells by stimulating the Na/K-ATPase, and the emergency treatment of hyperglycaemia with insulin may result in hypokalaemia. For this reason, the fluids infused intravenously during emergency treatment with insulin of severe hyperglycaemia in diabetic ketoacidosis should usually contain potassium.

(d) Probenecid

Probenecid is an organic acid, a benzoic acid derivative, which was developed to reduce the tubular secretion of penicillin and thus to delay the excretion of penicillin from the body, prolonging its therapeutic action. It inhibits the transport of organic acids across epithelial barriers and not only blocks the active secretion of penicillin into the renal tubular lumen, but also blocks the active reabsorption of uric acid. It has been used as a uricosuric agent in the treatment of gout, and occasionally to reduce the renal clearance of the penicillin s or cephalosporins from the blood, although this is usually achieved without probenecid, simply by increasing the dosage of antibiotic.

(e) Drugs that act on potassium channels

Potassium channels in cell membranes control the rate of efflux of potassium from the cells, and this tends to stabilize the transmembrane potential, according to the Nernst equation. Drugs that open potassium channels therefore reduce the likelihood of activation of the cell, while drugs that close potassium channels increase the likelihood of activation of the cell. Drugs that open potassium channels include vascular smooth muscle relaxants, such as minoxidil and hydralazine (used in the treatment of hypertension), and nicorandil (used in the treatment of angina pectoris). Drugs that block potassium channels include the sulfonylureas, which thereby increase the release of insulin from beta cells in the pancreas (used in the treatment of type 2 diabetes).

1.6. Drug action via enzyme inhibition

Many types of drug action can be produced by inhibition of enzymes, and the precise action will depend on the role that the inhibited enzyme plays in normal function. The following are illustrative examples of the ways in which drugs may act by inhibiting enzymes.

(a) Cholinesterase—neostigmine

Neostigmine is a reversible cholinesterase inhibitor. It is used in the treatment of myasthenia gravis because of its effect in increasing the concentration of acetylcholine at the muscle motor end-plate, thereby alleviating the block in neuromuscular transmission that occurs in this condition.

(b) Xanthine oxidase—allopurinol

Xanthine and hypoxanthine are oxidized to uric acid by the enzyme xanthine oxidase, which is inhibited by allopurinol. Allopurinol therefore reduces the synthesis of uric acid. This effect is produced mainly by its active metabolite, alloxanthine (or oxypurinol), which is a non-competitive inhibitor of xanthine oxidase. The reduction in uric acid production reduces the risks

of attacks of acute gouty arthritis, reduces the incidence of chronic gouty arthritis, and prevents the occurrence of uric acid stones (gouty nephropathy). Xanthine and hypoxanthine are considerably more water-soluble than uric acid, and their urinary excretion is rapid.

(c) Monoamine oxidase (MAO) inhibitors

Monoamine oxidase (MAO) inhibitors inhibit the metabolism of the monoamines 5-hydroxytryptamine, noradrenaline, and dopamine in the brain, and it is presumably by this action that they produce their antidepressant action. Isocarboxazid and phenelzine bind irreversibly to MAO, and new enzyme molecules must be synthesized in order to restore to normal the metabolism of monoamines, a process that takes about 2 weeks. In contrast, inhibition of MAO by tranylcypromine is reversible.

Just as drugs that act via receptors may be specific for one subtype of a receptor or another, so MAO inhibitors may be specific for one of the subtypes of MAO. For example, selegiline and rasagiline are specific inhibitors of MAO type B; they therefore inhibit the metabolism of dopamine in the brain and thereby enhance the action of levodopa in the treatment of Parkinson's disease. However, because MAO in the gut is principally of type A, these inhibitors do not produce the "cheese reaction" that other MAO inhibitors do. Moclobemide is a rapidly reversible inhibitor of MAO type A; it is used in the treatment of depression and has less propensity to produce the cheese reaction.

(d) Na/ K-ATPase—cardiac glycosides

The actions of the cardiac glycosides, such as digoxin, digitoxin, and ouabain, are secondary to inhibition of the sodium/potassium-activated adenosine triphosphatase (Na/K-ATPase, the Na/ K pump), a membrane-bound enzyme that is responsible for the major part of the active transport of potassium into cells and of sodium out of them, thus maintaining the normal high transmembrane gradients of these ions. This inhibition is thought to mediate the positive inotropic and chronotropic effects of cardiac glycosides, perhaps through a resultant rise in calcium concentrations within cardiac cells.

(e) Phosphoinositides—lithium

Lithium alters the turnover of the second messenger system involving phosphoinositides (see Figure 2) by inhibiting one of the enzymes of that system. However, it is not certain whether that is the mechanism whereby lithium produces its therapeutic effects in the treatment of manic-depressive illness.

(f) Phosphodiesterases—xanthines, milrinone, sildenafil

Phosphodiesterases are enzymes that cause the breakdown of cyclic AMP, as second messenger in receptor-mediated effects (see Figure 2). There are several different isoforms of phosphodiesterase in different tissues. The xanthines (for example theophylline) inhibit phosphodiesterase in the lung, causing bronchodilatation. However, this may not be their main mode of action as they also have actions at purine receptors. Milrinone and related compounds, such as enoximone, inhibit phosphodiesterase type 3, and have a positive inotropic effect on the heart; however, they increase mortality in heart failure and are used only in short-term therapy. Sildenafil and related compounds, such as avanafil, tadalafil, and vardenafil, inhibits phosphodiesterase type 5 in the corpus cavernosum in the penis, causing vasodilatation and hence penile erection.

(g) Other examples

Other drugs that act via enzyme inhibition include the following:

- some anticancer drugs, such as imatinib, that inhibit tyrosine kinase and other kinases;
- the anticancer drug cytarabine, which inhibits DNA polymerase;

- some anti-infective agents, which act by inhibiting bacterial or viral enzymes; for example, trimethoprim inhibits bacterial dihydrofolate reductase, the quinolones inhibit bacterial DNA gyrase, zidovudine and didanosine inhibit the reverse transcriptase of the human immunodeficiency virus (HIV), and oseltamivir and zanamivir inhibit influenza virus neuraminidase;
- aspirin and non-steroidal anti-inflammatory drugs, which inhibit the enzymes involved in prostaglandin synthesis;
- captopril and related drugs (ACE inhibitors), which inhibit the angiotensin-converting enzyme (ACE);
- coumarin anticoagulants, such as warfarin, which inhibit vitamin K epoxide reductase;
- other anticoagulants act as inhibitors of thrombin (factor II; argatroban, bivalirudin, dabigatran) or factor Xa (apixaban, fondaparinux, rivaroxaban);
- disulfiram, which inhibits aldehyde dehydrogenase, thus preventing the breakdown of aldehyde after the conversion of alcohol;
- drugs that inhibit viral RNA polymerase, such as sofosbuvir, which is effective against hepatitis C virus infection;
- drugs that inhibit viral serine protease, such as boceprevir, simeprevir, and telaprevir which are effective against hepatitis C virus infection.

(h) Adverse reactions

In some cases, the adverse effects of a drug can occur by enzyme inhibition. For example, procaine inhibits pseudocholinesterase and can enhance the actions of the depolarizing muscle relaxant succinylcholine. Metronidazole inhibits aldehyde dehydrogenase and can cause a disulfiram-like reaction to alcohol.

1.7. Drug action via direct enzymatic activity or the activation of enzymes

Just as some drugs act by inhibiting enzymes, so some drugs activate enzymes or themselves act as enzymes.

(a) Enzyme replacement in genetic and acquired enzyme deficiencies

Genetic diseases that are due to enzyme deficiencies should theoretically be susceptible to treatment by replacement of the enzyme or the gene. However, gene replacement therapy has so far proved disappointing and enzyme replacement therapy is limited by the difficulty of delivering enzymes to their sites of action. Nevertheless, clotting factor deficiencies can be treated in this way, good examples being the parenteral use of factor VIII in patients with haemophilia and of fresh frozen plasma or purified clotting factors in treating overdose with warfarin. Another example is the oral use of pancreatic enzymes in treating malabsorption in patients with chronic pancreatic insufficiency, using specially coated formulations plus antacids to reduce inactivation by gastric acid. Examples of enzymes that are used to treat or prevent illnesses or diseases associated with deficiencies are listed in Table 5.

Table 5. Examples of enzymes used to treat or prevent illnesses or diseases associated with deficiencies

Enzyme	**Deficiency disease**
Agalsidase	Fabry's disease
Alglucosidase alfa	Pompe's disease
Clotting factors	Haemophilia (factor VIII), Christmas disease (factor IX), etc
Galsulfase	Mucopolysaccharidosis type VI

Idursulfase	Mucopolysaccharidosis type II
Imiglucerase	Gaucher's disease types I and III
Lactase	Lactose intolerance
Laronidase	Mucopolysaccharidosis type I
Pancreatic enzymes	Exocrine pancreatic insufficiency
Velaglucerase alfa	Gaucher's disease type I

(b) Drugs acting on the clotting system

The clotting and fibrinolytic factors are enzymes, and certain drugs that act on clotting and fibrinolysis do so by increasing their activity. Heparin acts as an anticoagulant by activating antithrombin III. Streptokinase, urokinase, alteplase, and anistreplase are activators of plasminogen and thus cause clot lysis. Snake venoms, such as ancrod (Malayan pit viper venom), have thrombin-like activity and thus activate clotting.

(c) Cancer chemotherapy

L-asparaginase is an enzyme that hydrolyses asparagine, the consequent depletion of which in leukaemic cells is of benefit in some patients with acute lymphoblastic leukaemia.

(d) Other examples

Other examples of drugs that activate or replace enzymes include pralidoxime, which activates cholinesterase in poisoning with organophosphorus insecticides, and danazol and stanozolol, which increase the activity of the Cl esterase inhibitor in patients with hereditary angioedema.

1.8. Drug action via other miscellaneous effects

(a) Chelating agents

Drugs that chelate metals can be used to hasten the removal of those metals from the body, as the following examples show:

- calcium sodium edetate (ethylene diamine tetra-acetate or EDTA) chelates many divalent and trivalent metals and is used in the treatment of poisoning, particularly with lead;
- dimercaprol chelates certain heavy metals and is used in the treatment of mercury poisoning;
- deferoxamine chelates iron and is used in the treatment of iron poisoning and in the iron overload that occurs with repeated blood transfusion (for example in thalassaemia);
- penicillamine chelates copper and is used in the treatment of hepatolenticular degeneration (Wilson's disease), in which there is deposition of copper in the basal ganglia of the brain due to a deficiency of the copper-binding protein caeruloplasmin; it is also used to chelate cystine and thus prevent renal damage in cystinuria.

(b) Osmotic diuretics

Mannitol is a hexahydric alcohol related to mannose, and an isomer of sorbitol. It is freely filtered at the renal glomerulus but is reabsorbed to only a small extent by the renal tubules. It therefore increases the concentration of osmotically active particles in the tubular fluid and takes water with it, thus increasing urine volume. It has no other pharmacological effects. Mannitol has been used to produce a diuresis in the treatment of some types of acute poisoning and in cerebral oedema. It has sometimes been used to restore renal tubular function and urinary output in shock. Urea has a similar action to mannitol and has been used similarly in the treatment of cerebral oedema.

(c) Hormone analogues

Drugs that are analogues of hormones can produce similar effects to their endogenous counterparts. For example, the α-melanocyte-stimulating hormone analogue afamelanotide has been used to treat erythropoietic protoporphyria. Epoetins, which are analogues of the naturally

occurring hormone erythropoietin, are used to treat the anaemia of chronic renal insufficiency.

(d) Volatile general anaesthetics

These agents lack any obvious molecular feature in common. They form a diverse group of agents, such as the halogenated hydrocarbons (for example, halothane, desflurane, enflurane, and trichloroethylene), and non-halogenated agents (for example nitrous oxide and cyclopropane), which produce similar effects on the brain. The usual models of drug action do not readily accommodate this group of compounds. It is generally thought that their primary action is on the lipid matrix of the biological membrane, that the biophysical properties of the membrane are thereby changed, and that this results in changes in ion fluxes or other functions that are crucial for the normal operation of neuronal excitability.

(e) Replacement drugs

This is an artificial subheading pharmacologically, but one that is clinically useful. The best examples are oral and parenteral use of ferrous salts in the treatment of anaemia due to iron deficiency and intramuscular use of hydroxocobalamin (vitamin B_{12}) in the treatment of vitamin B_{12} deficiency, particularly as associated with pernicious anaemia. Compounds that are used to replace deficiencies are listed in Table 6. The use of hormones as replacement therapy (for example, thyroxine to replace natural thyroid hormone in hypothyroidism) could also be included under this heading, but is better included under the heading of drugs acting via a direct action on receptors, which is how hormones act. Similarly, the replacement of clotting factors, such as factor VIII in haemophilia, is better classified under the heading of actions via direct enzymatic activity.

Table 6. Examples of normal constituents of the diet used as dietary supplements to treat or prevent illnesses or diseases associated with deficiencies

Compound	**Deficiency disease**
Carnitine	Primary deficiency; valproate toxicity
Cereal starch	Glycogen storage disease
Cobalamins	Pernicious anaemia
Ferrous salts	Iron deficiency anaemia
Folic acid*	Folate deficiency
Vitamin C	Scurvy
Vitamin D analolgues	Osteomalacia and rickets
Zinc	Acrodermatitis enteropathica

*Also used in pregnancy to prevent neural tube defects, a use that is not relevant to this table

2. Stereoisomerism and drug action

The phenomenon of stereoisomerism of organic compound s was discovered by Louis Pasteur, following Jean Baptiste Biot's observation that when you shine polarized light through solutions of certain substances the light is twisted in one direction or another, a phenomenon known as optical activity. Pasteur showed that tartaric acid exists in two forms with different optical activities: one form rotates polarized light to the left and the other rotates it to the right. He did this after he had observed that tartaric acid crystals had two different shapes when viewed microscopically and separated the two types of crystals. This difference in the activity of two substances with exactly the same chemical composition is due to an asymmetry in one of the carbon atoms of tartaric acid, which results i n two structures that cannot be superimposed on top of one another (in the way that your left hand will not fit into a right-hand glove). An example of

stereoisomerism is shown in Figure 3. The central carbon atom in amino acids is asymmetrical i.e. it is attached to four different moieties, and two configurations are possible, mirror images of each other and not superimposable. Figure 3 shows this in the case of L-alanine and D-alanine. Levodopa (L-dihydroxyphenylalanine) has a similar structure to L-alanine, but the CH_3 group is replaced by $C_6H_3(OH)_2CH_2$.

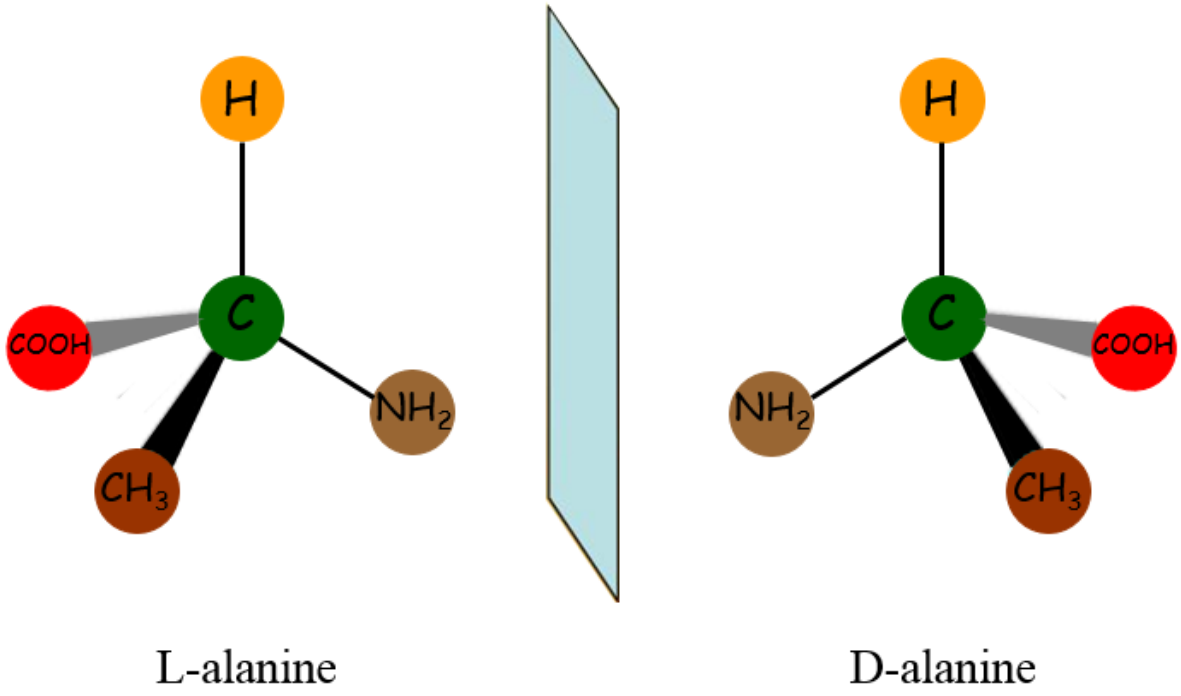

Figure 3. The two stereoisomers of the amino acid alanine

The terminology used to describe stereoisomers is complex. If a substance rotates polarized light to the right, it is called dextrorotatory and is designated by the letter d or by the symbol (+). If a substance rotates polarized light to the left, it is called laevorotatory and is designated by the letter l or by the symbol (–). A molecule may be either (+) or (–) depending on its milieu, since changes in factors such as pH, temperature, and the wavelength of the light used can affect the direction in which the light is rotated. However, these designations do not tell you anything about the actual spatial configuration of the molecules themselves, which is designated by other symbols: absolute configurations of chiral centres are designated by R and S (from the Latin "rectus" = right and "sinister" = left) and D and L (from the Latin "dexter" = right and "laevus" = left); relative configurations are designated by cis and trans (Latin words meaning "on this side" and "on the other side"), Z and E (German zusammen, together, and entgegen, opposite), and α and β.

Stereoisomers are of two types, enantiomers and diastereomers (or "epimers"). In enantiomers, asymmetry occurs either at a single centre of potential asymmetry (or "chiral" centre) if only one such centre exists in the molecule, or at more than one if more than one exists (in which case there will be more than two enantiomers). In diastereomers, asymmetry occurs at only one of the chiral centres, although the molecule has more than one chiral centre, and in such

cases the isomers are not mirror images of each other. Enantiomers have similar physicochemical properties to each other, while diastereomers do not. Chiral asymmetry is usually due to a carbon atom, but not in all cases, the asymmetrical phosphorus atom in cyclophosphamide being a case in point.

Examples of drug enantiomers are d-propranolol and 1-propranolol, R-warfarin and S-warfarin, L-glucose (laevulose) and D-glucose (dextrose), and cis-retinoic acid and all-trans-retinoic acid. Quinine and quinidine are diastereomers.

Of all synthetic drugs used in clinical practice, about 40 per cent are chiral and about 90 per cent of those are marketed in the racemic form (i.e. as an equal mixture of the two stereoisomers). Examples include d,1-propranolol and R,S-warfarin. Naproxen, esomeprazole, and escitalopram are examples of synthetic compounds that are marketed as single stereoisomers. In contrast, naturally occurring and semi-synthetic com pounds are almost all chiral and almost all are marketed as a single isomer. Examples include the naturally occurring amino acids (for example L-dopa) and D-glucose (dextrose).

The centre of asymmetry of a compound need not be in a part of the molecule that is important for the action of the drug, but if it is there will be pharmacological differences between the different stereoisomers, and these differences may be of clinical relevance. The following examples illustrate some of these differences.

2.1. Pharmacokinetic differences between stereoisomers

(a) Absorption

Both D-methotrexate and L-methotrexate are passively absorbed, but only to a small extent. However, L-methotrexate is also transported actively across the gut, while D-methotrexate is not. Thus, L-methotrexate is better absorbed that D-methotrexate.

(b) Distribution

The binding of d-propranolol to plasma albumin is more extensive than that of 1-propranolol. The binding of S-disopyramide to α_1-acid glycoprotein is more extensive than that of R-disopyramide. S-warfarin is more highly bound to albumin than R-warfarin, but R-warfarin is more highly protein bound overall than S-warfarin. These differences lead to differences in the distribution and rates of clearance of the different stereoisomers.

(c) Elimination

Numerous stereoisomeric differences in drug elimination have been described. For example, the first-pass hepatic metabolism of S-metoprolol is less than that of R-metoprolol. However, this is only the case in extensive hydroxylators of the debrisoquine type; in poor metabolizers, the first-pass metabolism of metoprolol is not affected by stereoisomerism.

Both the rates and the routes of metabolism of the stereoisomers of warfarin are different: the half-lives of S-warfarin and R-warfarin are 32 and 54 hours respectively, and the routes of metabolism are to 7-hydroxywarfarin for S-warfarin and to warfarin alcohols for R-warfarin.

The secretion of tocainide into the saliva is greater for R-tocainide than for S-tocainide.

2.2. Pharmacodynamic differences between stereoisomers

Stereoisomers are sometimes described as being active or inactive (the terms “eutomer” and “distomer” have also been used). For example, you could call the β-adrenoceptor antagonist 1-propranolol the active stereoisomer and d-propranolol, which is not a β-blocker, the inactive stereoisomer. However, to do so would be misleading, since d-propranolol has membrane-stabilizing activity like that of local anaesthetics. There are many other examples of stereoisomers that have different pharmacological actions from each other, and this is sometimes of clinical importance.

In some cases, a pharmacodynamic difference between stereoisomers is limited to a difference in potency; for example, S-warfarin is about five times more potent as an anticoagulant than R-warfarin. In other cases, the differences are differences in pharmacological and therapeutic actions. For example, 1-sotalol is a β-adrenoceptor antagonist while d-sotalol is a class III antiarrhythmic drug like amiodarone.

Sometimes the difference between stereoisomers is a difference between therapeutic and adverse effects. Nowhere is this seen more dramatically than in the example of thalidomide, whose R-stereoisomer is hypnotic but whose adverse effects seem to be due to the S-stereoisomer, which also has immunomodulatory actions.

Sometimes stereoisomeric differences tell you something about the mechanism of action of a drug. For example, S-timolol is a more potent β-adrenoceptor antagonist than R-timolol, but both are equally effective in reducing intraocular pressure in patients with glaucoma. This suggests that the mechanism of action whereby timolol lowers the intraocular pressure is not related to β-blockade; in fact, it seems to be due to calcium channel blockade.

2.3. Interactions between stereoisomers

Sometimes two stereoisomers interact with one another. For example, two stereoisomers can compete for binding to the same receptor, as in the case of methadone, whose S-stereoisomer antagonizes the respiratory depressant effect of the R-stereoisomer. If one stereoisomers is an agonist and the other an antagonist, the racemic mixture may appear to act as a partial agonist (see above, §1.1(c)).

In some cases, two stereoisomers are metabolically interconvertible. This is not uncommon with non-steroidal anti-inflammatory drugs of the arylalkanoic acid group, such as ibuprofen, most of whose R-stereoisomer is converted to the S-stereoisomer after administration.

2.4. Drug-drug interactions and stereoisomers

Some drug-drug interactions are stereoselective. For example, metronidazole, sulfinpyrazone, and phenylbutazone, which inhibit the metabolism of warfarin, primarily affect the more potent stereoisomer, S-warfarin.

2.5. The clinical relevance of stereoisomerism

There are no immediate practical consequences for routine drug therapy as a result of these observations, since the pharmacology and clinical pharmacology of drugs that are given as racemic mixtures have been worked out for the racemic mixtures. However, that is not to say that there are not important clinical consequences of the pharmacological differences between stereoisomers.

First, to neglect to study the pharmacology and clinical pharmacology of stereoisomers may be to miss some important facet of their clinical effects. This is exemplified by the elucidation of the complex interaction of phenylbutazone with warfarin. Phenylbutazone inhibits the metabolism of S-warfarin but induces the metabolism of R-warfarin. Thus, the clearance of the racemic mixture is unaffected, and this obscures the nature of the interaction. Further complication comes from the fact that the protein-binding displacement effect of phenylbutazone is also different for the two stereoisomers. Other warfarin interactions have similar stereoselectivity (e.g. the interaction with metronidazole).

Secondly, the use of pure stereoisomers might in some cases improve the quality of drug therapy, by more specific drug action and the avoidance of adverse drug reactions and interactions. For example, R-timolol might have an advantage over S-timolol or racemic timolol in the treatment of glaucoma, since it would be less likely to cause systemic β-blockade. Of course, such advantages would be offset in the cases of stereoisomers that are subject to

metabolic interconversion, but that is by no means a universal phenomenon.

3. Graded responses to drugs: the dose-response curve in drug therapy

According to the Law of Mass Action, the velocity of a chemical reaction depends on the concentrations of the reactants; when a chemical reaction reaches equilibrium, the concentrations of the chemicals involved bear a constant relation to each other, which is described by the equilibrium constant.

The pharmacological implication of this is that the pharmacological effect of a drug is related to the concentration of the drug at its site of action. The relationship between this concentration and the intensity of its pharmacological effect is called the dose-response curve, an example of which is shown in Figure 4.

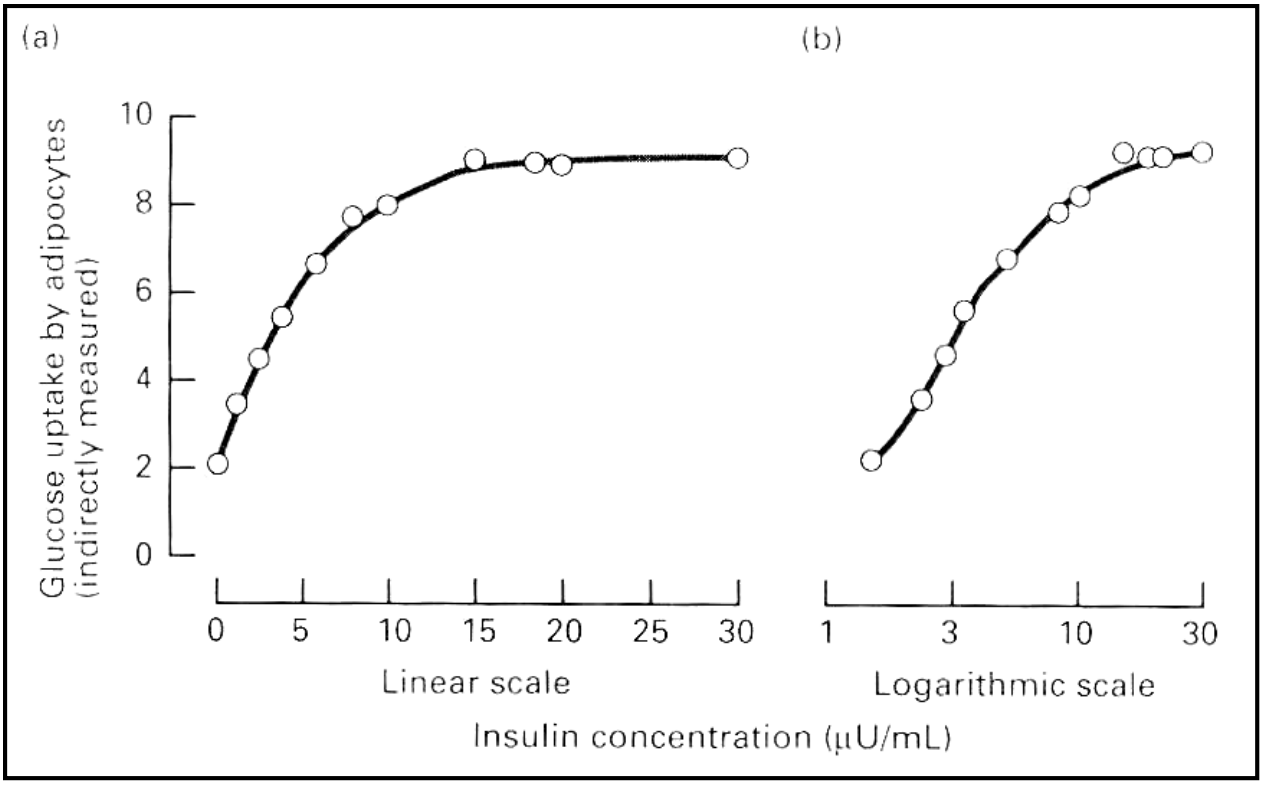

Figure 4. The relation between the concentration of insulin and its effect on glucose uptake by human adipocytes in vitro; (a) when the concentration scale is linear the curve is a rectangular hyperbola; (b) when the concentration scale is logarithmic the curve is sigmoid (Adapted from Cuatrecasas Proc Natl Acad Sci USA 1969; 63: 450-7.)

When there is no drug present there is no effect. As the drug is introduced and its concentration rises, so the pharmacological effect starts to occur and increases. Within certain limits, the higher the concentration the greater the pharmacological effect. However, there comes a point where the effect can no longer increase despite increasing concentrations.

Figure 4 illustrates an in vitro dose-response curve in isolated cells. In humans it is not usual to be able to define the dose-response curve in full—it is usually too difficult to measure the small effects produced by low doses or concentrations of drugs, and measurements cannot be

made at high doses or concentrations because of toxicity. It is therefore more usual to measure drug effects that occur in the middle of the curve. Thus, log dose-response curves are sometimes presented as being linear rather than sigmoid, since the middle part of a sigmoid curve, which spans approximately 20–80% of the maximum possible response, is roughly linear.

However, occasionally a complete dose-response curve can be delineated, and an example is shown in Figure 5, which shows the relations between the urinary concentrations of the loop diuretics bumetanide and furosemide and their diuretic effects. The urinary concentrations are shown because the site of action of these diuretics is on the luminal side of the renal tubule. This comparison of the dose-response curves for bumetanide and furosemide illustrates two aspects of drug action: potency and maximal efficacy. The potency of a drug is related to the amount of drug required to produce a given effect. In this case, bumetanide is 100 times more potent than furosemide mole for mole (70 times more potent mg for mg) since it takes a hundredth of the dose to produce the same natriuretic effect. However, both drugs have the same maximal efficacy; in other words, a high enough concentration of furosemide at its site of action will produce the same maximal effect on urinary sodium excretion as bumetanide, despite the difference in potency.

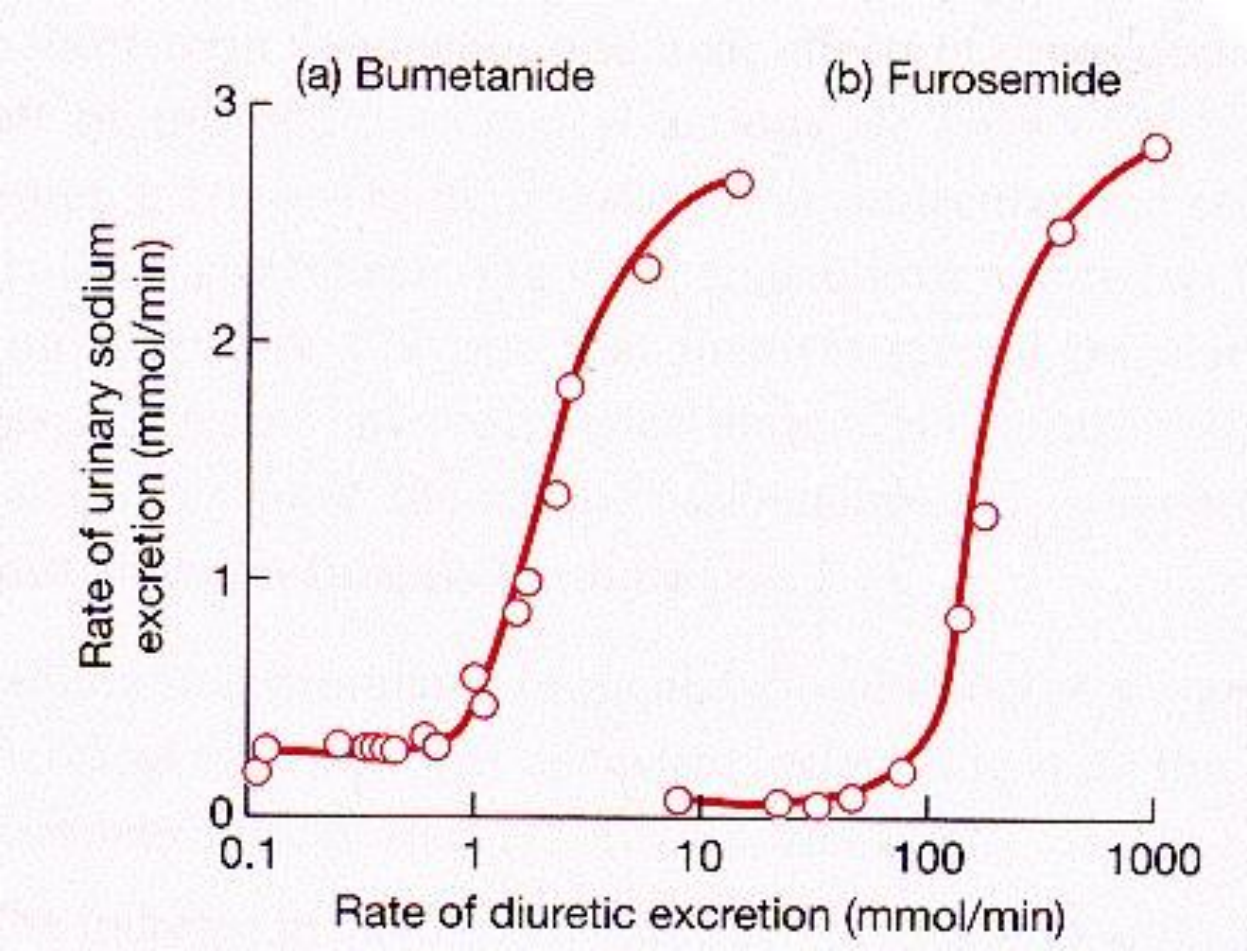

Figure 5. The relations between the urinary excretion rates of (a) bumetanide and (b) furosemide and their effects on the rate of sodium excretion in the urine. (Redrawn from Brater et al. Clin Pharmacol Ther 1983; 34: 207-13 (bumetanide) and Chennavasin et al. Pharmacol Exp Ther 1980; 215: 77-81 (furosemide))

When comparing drugs with each other, maximal efficacy is usually a more important criterion to consider than potency. If two drugs have different potencies you simply give a larger dose of the less potent drug, as in the case of bumetanide and furosemide. However, if two drugs have different maximal efficacies then the drug with the lower maximal efficacy will always produce a smaller maximal effect no matter how large the dose. For example, insulin has a much higher maximal efficacy than the oral hypoglycaemic drugs, whose effects in lowering blood glucose are relatively limited. The term "high ceiling diuretics" has been applied to the loop diuretics to indicate that they have a higher maximal efficacy than other diuretics, such as the thiazides.

However, sometimes relative potencies may also be of importance. This happens, for example, if the doses of two drugs which are equipotent on one system are not equipotent on another, as the following two examples illustrate.

1. Doses of bumetanide and furosemide that have equivalent effects on urinary sodium excretion do not have equivalent effects on the ear, bumetanide being less ototoxic. This is important when choosing a loop diuretic to use in combination with the aminoglycoside antibiotics, such as gentamicin, since furosemide is more likely than bumetanide to enhance their ototoxic effects. In these circumstances, bumetanide is the loop diuretic of choice.
2. Some β-adrenoceptor antagonists have different potencies in their actions on different subtypes of adrenoceptors. For example, atenolol is more potent as an antagonist at β_1-adrenoceptors than at β_2-adrenoceptors (i.e. it is a more selective β-blocker). This makes atenolol less likely than a non-selective drug, such as propranolol, to cause bronchospasm in a susceptible individual.

The concept of the therapeutic index of a drug, i.e. the toxic:therapeutic dose ratio, relies in part upon differential dose-response curves for therapeutic and toxic effects, as illustrated by these examples. The principles of the dose-response curve are at the core of accurate drug therapy, as the above observations illustrate, although at the clinical level it is sometimes hard to appreciate all the details. On the one hand, everyone can see that increasing doses of insulin produce increasing hypoglycaemia (i.e. insulin has high maximal efficacy) and that the dose-response relation changes with so-called insulin resistance (i.e. reduced potency) in the obese. It is not immediately apparent that the effectiveness of aspirin in the secondary prevention of myocardial infarction is rooted in dose-responsiveness, but it is nevertheless crucial in this indication. Aspirin binds covalently to and irreversibly inhibits cyclo-oxygenase, the enzyme in platelets that produces the precursor of thromboxane A2, which induces platelet aggregation. Platelets do not synthesize new cyclo-oxygenase, so the inhibition lasts for the life of the platelet. Repeated doses of aspirin therefore have a cumulative inhibitory effect on overall platelet aggregation. A daily dose of about 160 mg is usually enough to inhibit platelet cyclo-oxygenase completely. However, at this dosage, the synthesis of prostacyclin in vascular endothelium, which is a product of the eicosanoid pathway and both an inhibitor of platelet aggregation and a vasodilator, desirable properties in the prevention of coronary and cerebral thrombosis, is largely spared.

All of these examples illustrate only a few of the areas in which dose-responsiveness can be seen to be of clinical relevance.