**Introduction to Pharmacodynamics: The basis of drug therapy**

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Drugs and poisons are examples of pharmaceutically active substances. Drugs are medically useful, whereas poisons are toxic. Drugs should be identified by their INNs rather than by their brand names. There are significant cultural variances in the usage of a given substance between countries. Drugs should be categorised according to their mechanism of action, and conventional slang words should be avoided. Medicines are pharmaceutical formulations of substances intended for human use. Preclinical and clinical development are two stages in the transformation of a medication into a treatment. The latter is separated into three stages. Pharmacodynamics studies the impact of pharmacologically active chemicals on the human body. The most significant target classes for pharmaceuticals include receptors, enzymes, ion channels, and transporters. GPCRs, ligand-gated ion channels, and TK-linked receptors are the four types of receptors. Agonists stimulate receptors. Antagonists work by blocking the effects of agonists. Inhibitors inhibit the operation of enzymes and transporters. Blockers inhibit ion channel function whereas activators improve it. To evaluate the effects of medicines using the metrics EC50, IC50, and intrinsic activity, complete concentration-response relationships are necessary. The therapeutic index is a measure of a drug's safety. Many medications have a low therapeutic index and should thus be dosed cautiously. Some medications with a low therapeutic index are even accessible without a prescription.

**Keywords-**Pharmacodynamics;receptor agonist; Receptor antagonist**;** Enzyme/transporter inhibitor**;** Channel blocker**;** Drug development**;** Drug safety

1. **INTRODUCTION**

The study of a drug's molecular, biochemical, and physiologic effects or activities is known as pharmacodynamics. It is derived from the Greek terms "pharmakon," which means "medicine," and "dynamikos," which means "power." All medications exert their effects by interacting at the molecular level with biological structures or targets, causing a change in how the target molecule operates in relation to subsequent intermolecular interactions. These interactions include receptor binding, post-receptor effects, and chemical interactions.

(1) Drugs binding to an active site of an enzyme,

(2) Drugs that interact with cell surface signaling proteins to disrupt downstream signaling, and

(3) Drugs that act by binding molecules like tumor necrosis factor (TNF).

Effects are elicited as a result of the drug-target interaction, which can be assessed biochemically or clinically. Examples are (1) aspirin-induced platelet aggregation suppression, (2) ACE inhibitor-induced blood pressure decrease, and (3) insulin's blood-glucose-lowering impact. [1].

Pharmacodynamics is the study of medications' biochemical and physiological effects on the body, including drug action mechanisms and the relationship between drug concentration and effect. A common example of pharmacodynamics is how a drug quantitatively interacts with a drug receptor to elicit a reaction (effect). The molecules that engage with certain medications to cause a pharmacological action in the body are known as receptors. The different ways in which drugs produce their pharmacological effects are classified:

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 [2]

1. **DRUG ACTION VIA A DIRECT EFFECT ON A RECEPTOR**

Receptors are proteins that are found in cell membranes or, in rare situations, the cellular cytoplasm. There is a particular collection of medications or endogenous molecules (known as ligands) for each kind of receptor that are capable of binding to the receptor and creating a pharmacological action. The majority of receptors are found on the cell surface. Corticosteroids, which act on cytoplasmic steroid receptors, and 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, are two examples of drugs that act on intracellular receptors. The most significant receptor systems and ligands.

There are four types of ligand that act by binding to a cell surface receptor, agonists, antagonists, partial agonists, and inverse agonists [3].

**(a) Agonists**

Agonists are ligands that attach to a receptor and cause an appropriate reaction. The catecholamine adrenaline, for example, is an agonist at -adrenoceptors. It raises the heart rate by binding to -adrenoceptors in the heart.

**(b) Antagonists**

Antagonists are ligands that inhibit an agonist from attaching to a receptor and thereby preventing its effects. Antagonists do not have any pharmacological activities that are mediated by receptors. Propranolol, a -adrenoceptor antagonist, for example, binds to -adrenoceptors in the heart and reduces catecholamine-induced tachycardia (for example in response to exercise). In the absence of an agonist, however, propranolol has no impact on adrenoceptors [3].

**Table:** Examples of important receptors, their agonists and antagonists

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Receptor type | Subtype | | Site(s) in the body | Agonists | Antagonists |
| Adrenoceptors | | α/β |  | Adrenaline Noradrenaline | Labetalol |
| α1/α2 |  |  | Phentolamine  Phenoxybenzamine |
| α1 | Pupillary dilator muscle  Vascular smooth muscle | Dopamine (high doses) Phenylephrine | Doxazosin  Indoramin  Prazosin |
| α2 | CNS  Presynaptic nerve terminals | Clonidine | Yohimbine |
| β1/β2 |  | Dopamine  Isoprenaline | Propranolol  Oxprenolol |
| β1 | CNS  Heart | Dobutamine  Dopamine (moderate doses) | Atenolol  Metoprolol  Propranolol |
| β2 | Pancreatic islets  Smooth muscle  (bronchiolar, vascular, uterine) | Fenoterol  Rimiterol  Salbutamol  Terbutaline |  |
| Angiotensin | | AT1 | 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 (M1 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 (D2)  Metoclopramide  Phenothiazines (e.g. chlorpromazine)  Thioxanthenes (e.g. flupenthixol) |
| GABA  receptors | | GABAA-  BDZ complex | CNS | GABA  Benzodiazepines | Bicuculine |
| GABAB | CNS (presynaptic) | GABA | Baclofen |
| Histamine  receptors | | H1 | Smooth muscle (bronchiolar, vascular, gastrointestinal) | Histamine | Antihistamines  (e.g. promethazine, cetirizine) |
| H2 | Stomach | Histamine | Cimetidine  Ranitidine  Famotidine  Nizatidine |
| 5-Hydroxy-tryptamine receptors | | Various | CNS  Vascular smooth muscle  Gastrointestinal tract | 5HT | Methysergide (5HT)  Sumatriptan (5HT1D)  Ketanserin (5HT2)  Ondansetron (5HT3) |
| Leukotriene receptors | | CysLT1 | 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 | | V1A, V1b , andV2 |  | Vasopressin (ADH) | Conivaptan (V1A andV2)  Nelivaptan (V1b)  Tolvaptan (V2) |

**(c) Partial agonists**

When a sufficient number of receptors are bound, a complete agonist is capable of causing a maximum response. A partial agonist, on the other hand, cannot elicit the maximal response that the tissue is capable of producing, even though it binds to the same number of receptors that a full agonist binds to when producing a complete response. Because the effects of a ligand are generally produced by concentrations of the ligand far below those required to bind to all the receptors required to produce a complete response, a partial agonist may bind to receptors above a certain level of binding without producing any further increase in effect. However, by doing so, it may inhibit the activity of other agonists, giving the impression that it is behaving as an antagonist. This combination of activities is referred to as partial agonism. Oxprenolol, for example, a -adrenoceptor antagonist, is also a partial agonist. As a result, it may have less of an effect on heart rate slowing than adrenoceptor antagonists that do not exhibit partial agonist activity (i.e. full antagonists); this partial agonism of β-blockers is sometimes called “intrinsic sympathomimetic activity” (ISA) [3][4].

In the case of -adrenoceptor antagonists, the quantity of -blockade generated by a given dosage of the -blocker varies with the degree of endogenous sympathetic nervous system activity: the greater activity, the more -blockade produced by the action of a partial agonist. This is seen in the activities of xamoterol, a -adrenoceptor agonist/antagonist. In individuals with moderate heart failure, xamoterol works as a -adrenoceptor agonist, improving cardiac contraction. However, it serves as a -blocker in people with even mild heart failure, exacerbating the condition. As a result, sympathomimetic action has not proven beneficial in clinical practise." (ISA) [4].

Most receptors have subtypes for which certain ligands show some selectivity. For example, there are two kinds of -adrenoceptors known as 1 and 2, both of which may respond to adrenaline. Some -adrenoceptor antagonists work on both subtypes 1 and 2, whereas others are selective for one or the other. Propranolol, for example, is an antagonist at both 1 and 2 receptors, but atenolol is more selective for 1 receptors. It should be noted that this type of selectivity is just relative; whereas a medication like atenolol works predominantly on one receptor, at high enough doses it may also act on two receptors [3].

**(d) Inverse agonists**

An inverse agonist is a substance that binds to a receptor and elicits the opposite pharmacological reaction as the corresponding agonist. An agonist stimulates receptor activation, while an inverse agonist inhibits it. When the agonist is present, the inverse agonist functions as an antagonist. An ordinary antagonist can suppress both agonist and inverse agonists [4].

1. **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.

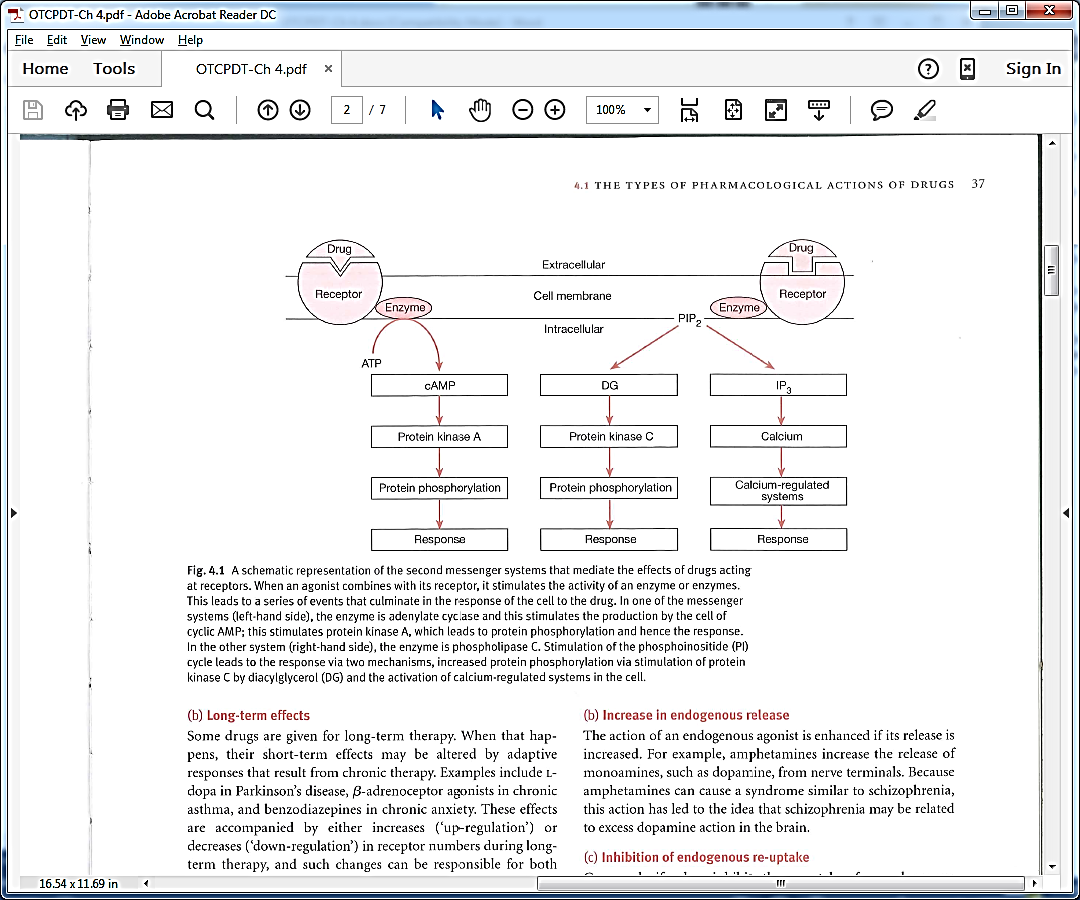
**(a) Short-term effects**

Many medications are utilised for their quick effects. Dopamine, for example, is utilised as a renal arteriolar vasodilator, diamorphine to reduce pain in cardiac ischaemia, and nebulized salbutamol to reverse bronchoconstriction in acute severe asthma. The receptors involved in the activity of a variety of receptors [5].

**i.** **Metabotropic receptors**

Many agonist medications act on cell surface receptors known as G protein-coupled receptors (GPCRs; also known as metabotropic receptors) and exercise their effects via what are known as second messenger systems. When a ligand attaches to a GPCR, the receptor undergoes a conformational change, allowing it to function as a guanine nucleotide exchange factor (GEF). It then activates a G protein linked with it by swapping its bound GDP for GTP.

The G protein subunit then dissociates from the and subunits and exerts effects on intracellular signalling proteins or target functional proteins directly depending on the subunit type. Gq11 stimulates phospholipase C whereas GS and Gi/o proteins activate adenylate cyclase and cAMP synthesis. The second messengers involved, as well as the G protein subtypes via which various receptors operate [6].



**Fig:** A schematic representation of the two types of second messenger systems that mediate the effects of drugs acting at G-protein coupled receptors

**ii. Ionotropic receptors**

Ionotropic receptors modulate neurotransmitter activities via secondary ion transport; the channels involved are known as ligand-gated ion channels (LGIC), which are membrane-bound proteins with a pore that permits chosen ions to flow following ligand binding. GABAA, glycine, and certain glutamate receptors are examples [7].

**iii. Nuclear receptors**

Nuclear receptors are specialized intracytoplasmic transcription factors that bind to specific response elements The response elements are in the promoter regions of certain target genes, whose transcription is therefore triggered or repressed, after ligand binding and transport to the nucleus. Corticosteroid, testosterone, thyroid hormone, vitamin D, and peroxisome proliferator activated receptors are a few examples [8].

**iv. Catalytic receptors**

Catalytic receptors are membrane-bound enzymes with a ligand binding site and a catalytic site that the ligand activates or inhibits. Angiotensin AT2, insulin, natriuretic peptide, prolactin, toll-like, and tumour necrosis factor receptors are a few examples [9].

**(b) Long-term effects**

When medications are used for long-term treatment, their short-term effects may be changed by adaptive responses caused by chronic therapy. Levodopa in Parkinson's illness, -adrenoceptor agonists in chronic asthma, and benzodiazepines in persistent anxiety are among examples. During long-term treatment, these effects are accompanied by either increases ("up-regulation") or decreases ("down-regulation") in receptor counts, and such changes can be responsible for both good and detrimental consequences [8].

**Soluble receptors**

Some receptors can be membrane-bound as well as soluble. The latter is often made up of the former's extracellular components. Cytokine receptors (e.g., tumour necrosis factor alfa, interleukin, and interferon receptors), growth hormone receptors, and erythropoietin and thrombopoietin receptors are examples of such receptors. Some soluble receptors form as a result of receptor down-regulation, as receptors degrade. Some are created as part of the receptor's regular activity and compete with the membrane-bound receptor for ligand binding [10].

Endogenous ligands can be prevented from attaching to their membrane-bound receptors by using soluble receptors, decreasing their cellular effects. Etanercept is an example of a fusion protein that contains a soluble TNF- receptor and is employed as a decoy receptor in the treatment of psoriasis and different forms of arthropathy[10].

1. **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 [10].

**(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 [11].

**(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 [12].

**(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 [11].

**(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 [12].

**(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 [13].

1. **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 [14].

**(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 co­transport, 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 [14].

**(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 [14].

**(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 [13].

**(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 [14].

**(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) [12].

1. **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 [15].

**(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 [15].

**(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 [15].

**(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 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 [15].

**(f) Phosphodiesterases—xanthines, milrinone, sildenafil**

Phosphodiesterases are enzymes that cause the breakdown of cyclic AMP, as second messenger in receptor-mediated effects. 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 angiotensin­converting 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 [15].

**(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. **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 [16].

**Table:** 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 [16].

**(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 [16].

**(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 [16].

1. **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 [17].

**(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 [17].

**(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 [17].

**(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 [17].

**(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 B12) in the treatment of vitamin B12 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 [16].

1. **DESIRED ACTIVITY**

The desired activity of a drug is mainly due to successful targeting of one of the following:

* Cellular membrane disruption
* Chemical reaction with downstream effects
* Interaction with enzyme proteins
* Interaction with structural proteins
* Interaction with carrier proteins
* Interaction with ion channels
* Ligand binding to receptors:
* Hormone receptors
* Neuromodulator receptors
* Neurotransmitter receptors

General anesthetics were once thought to work by disordering the neural membranes, thereby altering the Na+ influx. Antacids and chelating agents combine chemically in the body. Enzyme-substrate binding is a way to alter the production or metabolism of key endogenous chemicals, for example aspirin irreversibly inhibits the enzyme prostaglandin synthetase (cyclooxygenase) thereby preventing inflammatory response. Colchicine, a drug for gout, interferes with the function of the structural protein tubulin, while Digitalis, a drug still used in heart failure, inhibits the activity of the carrier molecule, Na-K-ATPase pump. The widest class of drugs act as ligands that bind to receptors that determine cellular effects. Upon drug binding, receptors can elicit their normal action (agonist), blocked action (antagonist), or even action opposite to normal (inverse agonist) [16].

In principle, a pharmacologist would aim for a target plasma concentration of the drug for a desired level of response. In reality, there are many factors affecting this goal. Pharmacokinetic factors determine peak concentrations, and concentrations cannot be maintained with absolute consistency because of metabolic breakdown and excretory clearance. Genetic factors may exist which would alter metabolism or drug action itself, and a patient's immediate status may also affect indicated dosage.

1. **UNDESIRABLE EFFECTS**

Undesirable effects of a drug include:

* Increased probability of cell mutation (carcinogenic activity)
* A multitude of simultaneous assorted actions which may be deleterious
* Interaction (additive, multiplicative, or metabolic)
* Induced physiological damage, or abnormal chronic conditions [17]

**Therapeutic window**

The therapeutic window is the amount of a medication between the amount that gives an effect (effective dose) and the amount that gives more adverse effects than desired effects. For instance, medication with a small pharmaceutical window must be administered with care and control, e.g. by frequently measuring blood concentration of the drug, since it easily loses effects or gives adverse effects [18].

**Duration of action**

The duration of action of a drug is the length of time that particular drug is effective. Duration of action is a function of several parameters including plasma half-life, the time to equilibrate between plasma and target compartments, and the off rate of the drug from its biological target [19].

1. **RECEPTORS SELECTIVITY**

Receptors are named on the basis of their major endogenous agonist (e.g. adrenergic, serotoninergic, opioid). They are then usually ‘sub-­‐typed’ on the basis of their selectivity for agonists or antagonists. Agonist selectivity is determined by the ratio of EC50 of the dose– response curve at the two different receptor subtypes. For example, β-­‐adrenoceptors can be sub-­‐typed into β1 and β2, on the basis of their responsiveness to the endogenous agonist, noradrenaline. The concentration required to cause bronchodilatation (via β2 adrenoceptors) is ten times higher than that required to cause tachycardia (via β1 adrenoceptors). Receptor sub-­‐ types can also be distinguished by the relative effectiveness of drugs that antagonize the effects of their full agonist, measured as the relative shift of the agonist dose–response curves achieved by a single dose of antagonist affecting responses mediated through the two receptors. It is important for prescribers to remember that selectivity for a receptor subtype is only a relative concept (i.e. selectivity does not equate with specificity) [20].

Agonist or antagonist drugs that are considered to be ‘selective’ for one receptor subtype can still produce significant effects at other subtypes if a high enough dose is given. This is particularly important if one receptor subtype activates the beneficial effects while another activates the adverse effects. For instance, ‘cardioselective’ β-­‐adrenoceptor blocking drugs have anti-­‐anginal effects on the heart (β1) but may cause bronchospasm in the lung (β2) and are absolutely contraindicated for asthmatic patients. Selectivity is useful in clinical practice only when the ratio of the impact of the drug at the two receptor sites is 100 or more. When selectivity is lower, it is difficult to predict drug doses that will exploit the difference in subtype activity [20].

1. **EFFICACY AND POTANCY**

Efficacy is the term used to describe the extent to which a drug can produce a response when all available receptors or binding sites are occupied (i.e. Emax on the dose–response curve). When comparing drugs acting at the same receptor, a full agonist will have the greatest efficacy and can produce the maximum response of which the receptor is capable. A partial agonist at the same receptor, by definition, will have a lower efficacy, even when all receptor sites are occupied. The concept of efficacy is not restricted to comparing the effects of drugs that act at the same receptor. The term therapeutic efficacy is used to describe the comparison of drugs that produce the same therapeutic effects on a biological system but do so via different pharmacological mechanisms (e.g. loop and thiazide diuretics, proton pump inhibitors and H2- antagonists). Potency is a term used to describe the amount of a drug required for a given response. More potent drugs produce biological effects at lower doses (or concentrations), which means that they have a lower ED50 [21].

The potency of a drug is related to its affinity for the receptor (i.e. how readily the drug-receptor complex is formed). Less potent drugs can have an efficacy similar to that of a more potent one; the difference in potency can be readily overcome by giving the less potent drug in higher doses. This is illustrated by the varying recommended dose ranges of drugs acting at the same drug target (e.g. H2 antagonists, ACE inhibitors).

When choosing between drugs with a similar beneficial effects (e.g. analgesia) from a group of similar drugs it might seem logical to choose the one with the greatest therapeutic efficacy. However, in some cases the most efficacious drug may be less favorable because the same mechanism of action that leads to clinical benefits may also be responsible for causing dose-limiting adverse-effects (e.g. opioids, β1-adrenoceptor blocking drugs). When the same action leads to both beneficial and adverse effects, the latter can be minimized by carefully increasing (titrating) the dose. However, some drugs have a steeper dose–response curve, which makes it more difficult to titrate to the dose that is effective but avoids adverse effects [21].

The potency of a drug is rarely a reason for choosing one out of a collection of drugs with similar beneficial therapeutic effects. This is because any differences in potency can be overcome simply by giving higher doses. Although differences in relative potency can be overcome by altered dosage, it should be remembered that most of the adverse effects of drugs are also dose-related. Potency may be relevant if these occur by a mechanism other than the receptor–ligand interaction that mediates the beneficial effect (because only the more potent drug will be active at concentrations that avoid unwanted adverse effects) [21].

For these reasons greater potency or efficacy does not necessarily mean that one drug is preferable to another. When judging the relative merits of drugs for a patient, prescribers should also consider other important factors, such as the overall adverse effect profile, therapeutic index, ease of administration for the patient, duration of effect (i.e. the number of doses needed each day) and cost [21].

1. **INTRODUCTION TO THE DOSE RESPONS RELATIONSHIP**

When the relation between drug dose (X-axis) and drug response (Y-axis) is plotted on a base 10 logarithmic scale, this produces a sigmoidal dose–response curve. This representation is more useful than a linear plot because it expands the dose scale in the region where drug response is changing rapidly and compresses the scale at higher doses where large changes have little effect on response. Clinical responses that might be plotted in this way include change in heart rate, blood pressure, gastric pH or blood glucose, as well as more subtle phenomena such as enzyme activity, accumulation of an intracellular second messenger, membrane potential, secretion of a hormone, or contraction of a muscle [22].

Progressive increases in drug dose produce increasing drug effects, but these occur over a relatively narrow part of the overall concentration range; further increases in drug dose (or concentration) beyond this range produce little extra effect. The clinical implication of this relationship is that simply increasing drug dose may not result in any further beneficial effects for patients and may cause adverse effects. The maximum response on the curve is referred to as the Emax and the dose (or concentration) producing half this value (Emax/2) is the ED50 (or EC50). The effective dose range can be considered as spanning the straight-line segment of the log dose–response curve (corresponding to 20–80% of Emax). The maximum tolerated dose is the highest dose of a drug that can be administered without the development of dose-related adverse effects [22].

The addition of a competitive antagonist to an agonist will lead to a shift in the agonist dose–response curve to the right because higher agonist concentrations are now required to achieve a given percentage receptor occupancy (and therefore effect). Dose–response curves of the agonist constructed in the presence of increasing doses of a competitive antagonist are progressively shifted to the right. Nevertheless, the effect of a reversible competitive antagonist can always be overcome by giving the agonist at a sufficiently high concentration (i.e. it is surmountable). Many clinically useful drugs are competitive antagonists (e.g. atenolol, naloxone, atropine, cimetidine). Non-competitive antagonists inhibit the effect of an agonist in ways other than direct competition for receptor binding with the agonist (e.g. by affecting the secondary messenger system). This makes it impossible to achieve maximum response even at very high agonist concentration. At a given concentration, non-competitive antagonists not only shift the agonist dose–response curve to the right but also decrease the Emax. Irreversible antagonists can be considered as a particular form of non-competitive antagonist characterized by antagonism that persists, even after the antagonist has been removed. Common examples are aspirin and omeprazole. This form of antagonism disappears only when new proteins or enzyme are synthesized. This explains why aspirin is effective, even when taken intermittently, as prophylaxis against cardiovascular events [23].

The dose-response relationship to the same drug varies between individuals because of various factors, such as differences in receptor number and structure, receptor-coupling mechanisms and physiological changes resulting from differences in genetics, age and health. For example, the effect of the loop diuretic, furosemide, is often significantly reduced at a given dose in patients with renal impairment. A further source of variability is that the same dose of drug does not achieve the same tissue drug concentrations in all individuals because of differences in handling (e.g. metabolism, excretion). In reality, it is this pharmacokinetic variation that explains most of inter-individual variation in drug response seen in clinical practice [23].

1. **REFERENCE**
2. Tozer, T. N., & Rowland, M. (2006). *Introduction to pharmacokinetics and pharmacodynamics: the quantitative basis of drug therapy*. Lippincott Williams & Wilkins.
3. Craig, W. A. (2014). Introduction to pharmacodynamics. In *Fundamentals of antimicrobial pharmacokinetics and pharmacodynamics* (pp. 3-22). Springer, New York, NY.
4. Thompson, S. A., Whiting, P. J., & Wafford, K. A. (1996). Barbiturate interactions at the human GABAA receptor: dependence on receptor subunit combination. *British journal of pharmacology*, *117*(3), 521-527.
5. Hoyer, D., & Boddeke, H. W. (1993). Partial agonists, full agonists, antagonists: dilemmas of definition. *Trends in pharmacological sciences*, *14*(7), 270-275.
6. Hurry, J., Lloyd, C., & McGurk, H. (2000). Long-term effects of drugs education in primary school. *Addiction Research*, *8*(2), 183-202.
7. Goudet, C., Magnaghi, V., Landry, M., Nagy, F., Gereau IV, R. W., & Pin, J. P. (2009). Metabotropic receptors for glutamate and GABA in pain. *Brain Research Reviews*, *60*(1), 43-56.
8. McGehee, D. S., & Role, L. W. (1996). Presynaptic ionotropic receptors. *Current opinion in neurobiology*, *6*(3), 342-349.
9. Francis, G. A., Fayard, E., Picard, F., & Auwerx, J. (2003). Nuclear receptors and the control of metabolism. *Annual review of physiology*, *65*, 261.
10. Alexander, S. P., Mathie, A., & Peters, J. A. (2007). Catalytic receptors. *British Journal of Pharmacology*, *150*(Suppl 1), S122.
11. Lohmann, A. B., & Welch, S. P. (1999). ATP-gated K+ channel openers enhance opioid antinociception: indirect evidence for the release of endogenous opioid peptides. *European journal of pharmacology*, *385*(2-3), 119-127.
12. Johnson, G. E. (1896). Physiological Antagonism. *The Dental Register*, *50*(8), 369.
13. Morris, M. J., & Pavia, J. M. (2004). Increased endogenous noradrenaline and neuropeptide Y release from the hypothalamus of streptozotocin diabetic rats. *Brain research*, *1006*(1), 100-106.
14. Guhlmann, A. L. B. R. E. C. H. T., Keppler, A. N. D. R. E. A., Kästner, S., Krieter, H., Brückner, U. B., Messmer, K., & Keppler, D. (1989). Prevention of endogenous leukotriene production during anaphylaxis in the guinea pig by an inhibitor of leukotriene biosynthesis (MK-886) but not by dexamethasone. *The Journal of experimental medicine*, *170*(6), 1905-1918.
15. Galvele, J. R. (1976). Transport processes and the mechanism of pitting of metals. *Journal of the Electrochemical Society*, *123*(4), 464.
16. Antao, A. M., Tyagi, A., Kim, K. S., & Ramakrishna, S. (2020). Advances in deubiquitinating enzyme inhibition and applications in cancer therapeutics. *Cancers*, *12*(6), 1579.
17. Salvemini, D., Misko, T. P., Masferrer, J. L., Seibert, K., Currie, M. G., & Needleman, P. (1993). Nitric oxide activates cyclooxygenase enzymes. *Proceedings of the National Academy of Sciences*, *90*(15), 7240-7244.
18. RICHARDSON, D. W., & ROBINSON, A. G. (1985). Drugs five years later: desmopressin. *Annals of internal medicine*, *103*(2), 228-239.
19. Zivin, J. A. (1998). Factors determining the therapeutic window for stroke. *Neurology*, *50*(3), 599-603.
20. Zimmerman, T. J., & Kaufman, H. E. (1977). Timolol: Dose response and duration of action. *Archives of Ophthalmology*, *95*(4), 605-607.
21. Xi, Z. X., & Gardner, E. L. (2007). Pharmacological actions of NGB 2904, a selective dopamine D3 receptor antagonist, in animal models of drug addiction. *CNS drug reviews*, *13*(2), 240-259.
22. Howarth, P. H. (1999). Assessment of antihistamine efficacy and potency. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology*, *29*, 87-97.
23. Alberts, A. S., Smit, B. J., Louw, W. K., van Rensburg, A. J., van Beek, A., Kritzinger, V., & Nel, J. S. (1997). Dose response relationship and multiple dose efficacy and toxicity of samarium-153-EDTMP in metastatic cancer to bone. *Radiotherapy and oncology*, *43*(2), 175-179.
24. Busso, T. (2003). Variable dose-response relationship between exercise training and performance. *Medicine & Science in Sports & Exercise*, *35*(7), 1188-1195.