INTRODUCTION TO PHARMACODYNAMICS: THE BASIS OF DRUG THERAPY

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ABSTRACT

Drugs and poisons are examples of compounds used in pharmaceuticals. Drugs are medically beneficial but poisons are toxic. Instead of using brand names to identify medications, INNs should be employed. The way that a particular medicine is utilized in several nations varies greatly depending on cultural norms. Drugs should be categorized based on how they work rather than using outdated slang labels. Pharmaceutical formulations of chemicals intended for human consumption are known as medicines. The two steps involved in developing a medication into a medicine are preclinical and clinical development. The latter is split into three parts. The study of pharmacologically active substances' effects on the human body is known as pharmacodynamics. The most crucial target classes for pharmaceuticals include receptors, enzymes, ion channels, and transporters. GPCRs, ligand-gated ion channels, and TK-linked receptors are among the four different types of receptors. Angiogenesis function by activating receptors. The way antagonists work is to counteract the effects of agonists. Inhibitors stop the action of enzymes and transporters. Blockers prevent ion channel function from occurring, whereas activators promote it. To assess the effects of medications using the metrics EC50, IC50, and intrinsic activity, complete concentration-response relationships are necessary. A drug's safety is evaluated by the therapeutic index. Many drugs should only be dosed with care since they have a poor therapeutic index. Some medications with a low therapeutic index are even sold over the counter.

Keywords: Pharmacodynamics; Receptor Agonist; Enzyme/Transporter Inhibitor; Channel Blocker; Drug Development; Drug Safety

I.INTRODUCTION

Pharmacodynamics is the study of the molecular, biochemical, and physiological responses of the body to medications. The words "pharmakon" (medicine) and "dynamikos" have their Greek sources (power). All drugs work by interfering with biological structures or targets on a molecular level, changing how the target molecule responds to subsequent intermolecular interactions. Examples of these connections include receptor binding, post-receptor effects, and chemical interactions.

(1) Drugs that bind to the active site of an enzyme,
(2) Drugs that affect downstream signaling by interacting with cell surface signaling proteins, and
(3) Drugs that work by binding to molecules, such as tumor necrosis factor (TNF).

It is possible to evaluate drug-target interactions biochemically or clinically. Examples include the effects of aspirin on platelet aggregation, ACE inhibitors on blood pressure, and insulin on blood glucose levels [1].

Pharmacodynamics is the study of how drugs interact with the body biochemically and physiologically, including how they work and how concentration and effect are related. How a substance interacts with a drug receptor quantitatively to cause a response is a simple illustration of pharmacodynamics (effect). Receptors are molecules that interact with specific drugs to produce pharmacological effects in the body. The various pharmacological processes that drugs might affect are divided into the following categories:

1.Drug activity through a receptor: antagonists, agonists, partial antagonists, inverse antagonists, and agonists.
2. Drug action through indirect modification of an inherent agonist's influence
(a) Physiological antagonism
(b) Inhibition of endogenous re-uptake

(c) Inhibition of endogenous metabolism
(d) Inhibition of endogenous release prevention
(e) Inhibition of endogenous metabolism
3. Drug suppression through transportation processes
4. Drug action through enzyme inhibition
5. Drug action by the activation of enzymes or enzymatic activity
6. Drug activity through a variety of side effects, including chelating agents, osmotic diuretics, volatile general anesthetics, and replacement drugs. [2]

II. DRUGS THAT ACT DIRECTLY ON A RECEPTOR

Receptors are proteins that can occasionally be found in the cytoplasm of cells or in cell membranes. A distinct set of pharmaceuticals or endogenous molecules (referred to as ligands) can bind to each type of receptor and result in pharmacological action. On the cell surface, receptors can be present in the majority. Corticosteroids, which operate on cytoplasmic steroid receptors, and thiazolidinediones, like pioglitazone, which activate PPARy, a nuclear receptor thought to be important in the expression of genes related to lipid metabolism and insulin sensitivity, are examples of intracellular receptor medicines. The most important ligands and receptors
Agonists, partial agonists, inverse agonists, and agonists are the four categories for ligands that function by binding to a cell surface receptor [3].

- **Agonist**

Ligands that bind to a receptor and trigger a response are known as antagonists. For instance, the catecholamine adrenaline is an agonist at -adrenoceptors. It induces the heart to beat more quickly by attaching to -adrenoceptors.

- **Antagonist**

An agonist's effects are inhibited by antagonists, which work by preventing an agonist from binding to a receptor. The pharmacological effects of antagonists are not receptor-mediated. The heart's -adrenoceptors are bound by the -adrenoceptor antagonist propranolol, which lowers catecholamine-induced tachycardia (for example in response to exercise). Contrarily, propranolol does not affect adrenoceptors in the absence of an agonist **[3].**

Table: Important receptors, their agonists, and their antagonists, as examples

Receptor type	Subtype	Site(s) in the body	Agonists	Antagonists
Adrenoceptors	α/β		Epinephrine Nonepinephrine	labetalol hydrochloride
	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	Dopamine Dobutamine (moderate doses)	Metoprolol Atenolol Propranolol
	β_2	islets of the pancreas supple muscle (bronchiolar, vascular, uterine)	Fenoterol Salbutamol Rimiterol Terbutaline	

Angiotensin	AT_1	Cardiovascular	Angiotensin	Eprosartan Losartan Irbesartan Pirenzepine (M_1 selective) Valsartan
Cholinoceptors	Muscarinic	tissues that parasympathetic nerves innervate	Acetylcholine and its derivatives (e.g. carbachol, bethanecol)	Atropine and analogues Orphenadrine Quinidine Tricyclic antidepressants Trihexyphenidyl
	Nicotinic	the neuromuscular junction Ganglia contain postganglionic cells.	Acetylcholine and a few of its analogues, like carbachol,)	Ganglion-blocking drugs Neuromuscular-blocking drugs Quinidine Aminoglycoside antibiotics
Dopamine receptors	Various	CNS Renal vasculature	Apomorphine Bromocriptine Dopamine (low doses	Metoclopramide Butyrophenones (e.g. haloperidol) Phenothiazines (e.g. chlorpromazine) Thioxanthenes (e.g. flupenthixol)
GABA receptors	$GABA_A$-BDZ complex	CNS	**Gamma-aminobutyric acid** (GABA)Benzodiazepines	Bicuculine
	$GABA_B$	CNS (presynaptic)	**Gamma-aminobutyric acid** (GABA)	Baclofein
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	Vessel smooth muscle in the CNS the digestive system	5HT	Methysergide (5HT) Sumatriptan ($5HT_{1D}$) Ketanserin ($5HT_2$) Ondansetron ($5HT_3$)
Leukotriene receptors	$CysLT_1$	vascular smooth muscle and bronchial muscle	Leukotrienes	Montelukast Zafirlukast
Opioid receptors	Δ, μ , and κ	Biliary system the urinary tract Muscle with pimples Muscle of the vasculature the digestive system CNS	Drugs that are not opioids (agonists, such as pentazocine)Morphine and analogues (μ agonists) Endorphins and enkelphalins	Naloxone (δ and κ) Nalbuphine (μ, δ, and κ) Nalorphine (μ) Buprenorphine (κ) (partial agonist) Naltrexone (μ, δ, and κ)
Vasopressin receptors	V_{1A}, V_{1b} , and V_2		Vasopressin (ADH)	Nelivaptan (V_{1b}) Conivaptan (V_{1A} and V_2) Tolvaptan (V_2)

- **Partial agonists**

A full agonist can generate the maximum reaction when enough receptors are bound. In contrast, while binding to the same number of receptors as a full agonist when producing a complete response, a partial agonist cannot evoke the maximal response that the tissue is capable of producing. Because the effects of a ligand are frequently accomplished at concentrations far lower than those required to A partial agonist may bind to receptors over a particular level of binding without increasing the effect further. This is because it does not need to bind to all of the receptors necessary to produce a full response. It may, however, inhibit the effect of other agonists in this way, giving the impression that it is working as an antagonist. This combination of behaviors is referred to as partial agonism. Oxyprenolol, for A partial agonist is, for instance, a -adrenoceptor antagonist. This partial agonism of -blockers is referred to as "intrinsic sympathomimetic activity" (ISA), and it may have less of an impact on heart rate slowing than adrenoceptor antagonists with no partial agonist action (i.e., full antagonists) [3][4].

The amount of -blockade produced by a specific dose of an antagonist for the -adrenoceptor varies depending on how active the endogenous sympathetic nervous system is.: The influence of a partial agonist causes more -blockade the more activity there is. This is demonstrated by the -adrenoceptor agonist/antagonist Xamoterol. Xamoterol improves cardiac contraction in patients with moderate heart failure by acting as a -adrenoceptor agonist. In people with even mild heart failure, it acts as a -blocker, aggravating the issue. Therefore, it has been shown that sympathomimetic activity is useless in practical practice. (ISA) [4].

There are subtypes of most receptors that are selective for particular ligands. Adrenoceptors come in two varieties, 1 and 2, and both can react to adrenaline. While some -adrenoceptor antagonists only affect one subtype, others affect both subtypes 1 and 2. Atenolol is more selective for 1 receptors than propranolol, which is an antagonist of both 1 and 2 receptors. The fact that this type of selectivity is just relative should be emphasized. For instance, atenolol normally acts on one receptor, but at sufficiently high doses, it may also act on two receptors [3].

- **Inverse agonists**

An inverse agonist is a substance that binds to a receptor and triggers the exact opposite pharmacological reaction as its corresponding agonist. An agonist increases receptor activity, whereas an inverse agonist decreases it. The inverse agonist acts as an antagonist when the agonist is present. An agonist and an inverse agonist can both be suppressed by an ordinary antagonist [4].

III. DRUGS' SHORT-TERM AND LONG-TERM IMPACTS AT RECEPTORS

Drugs and endogenous substances can have either long-term or short-term pharmacological effects.

1. Short-term effects

Drugs are frequently used due to their quick effects. For instance, diamorphine is used to treat discomfort associated with cardiac ischemia, dopamine acts as a renal arteriolar vasodilator, and nebulized salbutamol reverses bronchoconstriction in patients with severe asthma. The receptors that have a role in how certain receptors work [5].

- **Metabotropic receptors**

Many agonist medications exert their effects via second messenger systems by binding to cell surface receptors known as G protein-coupled receptors (GPCRs; also known as metabotropic receptors). A ligand's shape changes when it binds to a GPCR, enabling it to serve as a guanine nucleotide exchange factor (GEF). After that, it switches GDP for GTP to activate a similar G protein.

Many agonist drugs work by attaching to G protein-coupled receptors on cell surfaces, which are second messenger systems (GPCRs; also known as metabotropic receptors). When a ligand connects to a GPCR, its shape changes, allowing it to function as a guanine nucleotide exchange factor (GEF). In order to activate a related G protein, it then changes GDP for GTP. Phospholipase C is activated by Gq11, whereas adenylate cyclase and cAMP production are activated by GS and Gi/o proteins. Second messengers are implicated, as are the G protein subtypes via which many receptors work [6].

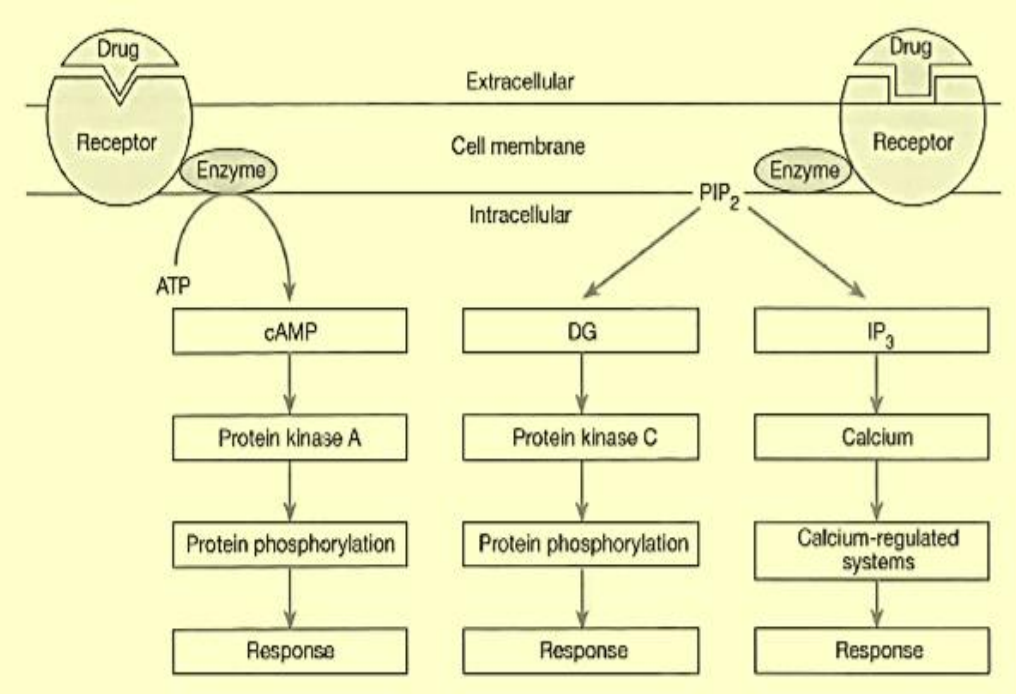

Fig: An illustration of the two kinds of second messenger systems that mediate how medications acting on G-protein coupled receptors affect the body.

- **Ionotropic receptors**

Secondary ion transport is a mechanism by which ionotropic receptors regulate neurotransmitter activity. The channels involved are ligand-gated ion channels (LGIC), which are membrane-bound proteins with a pore that opens in response to ligand binding. GABAA, glycine, and certain glutamate receptors are a few examples [7].

- **Nuclear receptors**

Nuclear receptors are intracytoplasmic transcription factors that bind to particular response areas and have unique roles. The target genes' transcription is consequently either triggered or repressed after ligand binding and delivery to the nucleus thanks to the response elements' location in their promoter regions. The following are some examples: peroxisome proliferator activated receptors, thyroid hormone, testosterone, corticosteroids, and vitamin D [8].

- **Catalytic receptors**

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

2. Long-term effects

The adaptive reactions brought on by continued therapy may alter the short-term effects of drugs when they are used as long-term treatments. Examples include levodopa for Parkinson's disease, -adrenoceptor agonists for chronic asthma, and benzodiazepines for persistent anxiety. The receptor numbers either rise ("up-regulation") or fall ("down-regulation") over time as a result of these processes, which can have both positive and negative impacts [8].

- **Soluble receptors**

Some receptors can be soluble as well as membrane-bound. The extracellular components of the former are typically found in the latter. These receptors include erythropoietin and thrombopoietin receptors, growth hormone receptors, and cytokine receptors (such as tumour necrosis factor alfa, interleukin, and interferon

receptors). Some soluble receptors emerge as a result of receptor down-regulation as receptors degrade. Some are created as part of the receptor's regular operation and compete with the membrane-bound receptor for ligand binding [10].
By employing soluble receptors, endogenous ligands can be inhibited from connecting to their membrane-bound receptors, reducing their cellular effects Psoriasis and other arthropathies are treated with etanercept, a fusion protein that contains a soluble TNF- receptor and functions as a decoy receptor [10].

IV.DRUG ACTION THOUGH INDIRECT MODIFICATION OF AN ENDOGENOUS AGONIST'S RESULT

The effects of an endogenous agonist may change in indirect ways, much as an antagonist would produce a therapeutic response by directly counteracting the action of an endogenous agonist [10].

(a) Physiological antagonism

A medication that mimics the physiological effect of an agonist can operate as an indirect antagonist to that agonist's action. For instance, endocrine may function as a physiological antagonist to the effects of a hypoglycemic drug and be used to treat symptoms brought on by insulin [11].

(b) Augmented endogenous unharness

If an endogenous agonists unharness is boosted, its effect is amplified. As an illustration, amphetamines enhance the release of monoamines from nerve terminals, such as Intropin. Due to the fact that amphetamines can produce a condition that is similar to schizophrenic psychosis, this action has led researchers to hypothesis that excess Intropin action in the brain may also contribute to schizophrenic psychosis [12].

(c) Inhibition of endogenous re-uptake

On the other hand, a drug's effects will be enhanced if it prevents the uptake of an endogenous agonist. As an illustration, several antidepressants, such as selective monoamine neurotransmitter uptake inhibitors and antidepressant drugs, prevent the uptake of neurotransmitters like serotonin and vasoconstrictor by neurons [11].

(d) Inhibition of endogenous metabolism

A drug's effects will be enhanced if it prevents the metabolism of an endogenous agonist. For instance, the MAO (MAO) inhibitors enhance the effects of monoamines by inhibiting the metabolism of catecholamine and vasoconstrictor [12].

(e) Hindrance of endogenous unharness

The effects of an endogenous agonist can be reduced by preventing its release. Inhibiting the release of inflammatory mediators from mast cells within the lungs is one of the intended ways through which cromones, like Na cromoglicate, turn out its therapeutic actions in respiratory disease. Angiotensin-converting protein (ACE) inhibitors prevent the production of angiotonin II, which lowers the endogenous release of mineralocorticoids, which in turn causes K retention [13].

V. DRUG ACTION THROUGH TRANSPORT PROCESS INHIBITION

Because cations (like Na, potassium, and calcium) and other substances (like organic acids in the kidneys and neurotransmitters in the nervous system) are transported and disposed in such crucial ways for the maintenance of conventional cellular functions, interfering with their transport may be a common drug mechanism. The following are a few examples of how drugs may work by impairing transport processes [14].

(a) Diuretics

Many diuretics work by limiting Na resorption within the excretory organ tubules, but the ways vary. The loop diuretics water pill and bumetanide, as an exampleoperate at the phenobarbitone surface of the ascending limb of the loop of Henle by inhibiting the Na/K/Cl cotransport mechanism, which is responsible for the simultaneous movement of Na, K, and Cl across cell membranes. Amiloride, a potassium-sparing water pill, works

by interference Na channels within the distal convoluted tube-shaped structure. water pill water pills work by interference the Na/Cl co-transport mechanism within the distal convoluted tubule's proximal section though the bulk of the diuretic impact of internal organ glycosides is thanks to augmented flow and therefore augmented excretory organ blood flow, a little of its activity is thanks to inhibition of excretory organ hollow Na/K-ATPase. However, certain diuretics work by mechanisms other than ones that have a direct impact on transportation networks. In the distal convoluted tube-shaped structure, corticoid, for instance, may function as a competitive antagonist at mineralocorticoid receptors, whereas acetazolamide is a protein that inhibits carbonaceous anhydrase activity in the proximal convoluted tube-shaped structure [14].

(b) Metal channel blockers

Calcium channel blockers, including dihydropyridines, diltiazem, and calcium blockers (such as calcium-channel blocker and amlodipine), work by reducing metal transmembrane transport across cell membranes via potential-operated L-type metal channels. as a result of metal plays numerous vital roles in these tissues, totally different|the various} The most important of them are a medication effect within the heart (such as verapamil) and a vasodilative action on peripheral arterioles because different medications have varied specificities for metal channels in various tissues and because metal plays several key functions in these tissues (for example nifedipine). A T-type metal channel blocker called mibefradil that didn't cause reflex cardiac arrhythmia (unlike L-type channel blockers), was accustomed treat cardiovascular disease however was removed off the market thanks to many unfavorable drug-drug interactions [14].

(C) Hypoglycemic Agent

One of insulin's various functions is to spice up the inward flow of aldohexose into cells, that is mediate by hypoglycemic agent receptors. the short decline in blood sugar iatrogenic by hypoglycemic agent within the treatment of hyperglycemia in polygenic disease is probably going because of this activity. hypoglycemic agent stimulates the Na/K-ATPase, that promotes AN inward flow of K into cells, therefore emergency treatment of hyperglycemia with hypoglycemic agent might end in hypokalemia. As a result, fluids injected intravenously throughout emergency hypoglycemic agent medical aid of utmost hyperglycemia in diabetic acidosis ought to usually contain K [13].

(d) Medication

A carboxylic acid byproduct called probenecid was created to impede the hollow secretion of antibiotics, which would delay the drugs' expulsion from the body and prolong their therapeutic action. It doesn't just stop the active antibiotic medicine from being secreted into the excretory organ hollow lumen; it also inhibits the transfer of organic acids across animal tissue barriers. However conjointly prevents active acid resorption. it's been used as a uricosuric drug within the treatment of urarthritis, further on slow the excretory organ clearance of penicillin or cephalosporins from the blood, but this is often ordinarily accomplished while not medication, just by raising the antibiotic indefinite quantity [14].

(e) Medication that act on atomic number 19 channels

The transmembrane potential is said to be stabilised by atomic number 19 channels in cell membranes, which limit the pace of atomic number 19 flow from the cells. Medications that open atomic number 19 channels diminish the prospect of cell activation, whereas medication that block atomic number 19 channels increase the danger of cell activation. vascular sleek muscle relaxants like vasodilator and vasodilative (both used to treat hypertension) and nicorandil area unit samples of medication that open atomic number 19 channels (used within the treatment of angina pectoris). Sulfonylureas area unit medication that block atomic number 19 channels, boosting the output of internal secretion from the duct gland's beta cells (used in the treatment of type 2 diabetes) [12].

VI. DRUG ACTION THROUGH PROTEIN INHIBITION

The real activity may depend on the function that the inhibited protein performs in routine operation. Enzymes may stop inhibiting during a variety of medical specialist acts. The samples that follow illustrate how various drugs might inhibit enzymes.

(a) Cholinesterase—neostigmine

Neostigmine may possibly be a reversible enzyme substance. Because it will raise the concentration of neurotransmitter at the muscle motor end-plate, lessening the block in contractor transmission that occurs during this illness, it is used to treat diseases of the neuromuscular junction [15].

(b) Organic compound oxidase—allopurinol

The protein organic compound enzyme, that is blocked by Zyloprim, oxidises organic compound and hypoxanthine to acid. As a result, Zyloprim lowers acid production. This result is often caused by alloxanthine (or oxypurinol), It could be a non-competitive organic chemical enzyme substance. Inhibiting the formation of acid stones and reducing the likelihood of acute urarthritis episodes are all benefits of reduced acid production (gouty nephropathy). Organic compounds and hypoxanthine have a quick excretory product excretion and are somewhat more soluble than acids [15].

(c) MAO (MAO) inhibitors

The action of antidepressant medications is thought to be produced by monoamine oxidase (MAO) inhibitors, which prevent the metabolism of the monoamine's serotonin, norepinephrine, and intropin inside the brain. Monoamine oxidase inhibitor and MAOI bind to MAO irreversibly, and new protein molecules should be synthesized to revive traditional amine metabolism, a method that takes concerning a pair of weeks. monoamine oxidase inhibitor, on the opposite hand, inhibits MAO throughout a reversible manner.
While drugs that operate on receptors are also selective for one subtype of a receptor or another, MAO inhibitors may even be specific for one in every one of the subtypes of MAO. Selegiline and rasagiline, as an illustration, are MAO B inhibitors that impede the metabolism of Intropin in the brain and so improve the effectiveness of L-dopa in the treatment of encephalopathy. These inhibitors do not, however, cause the "cheese response" that other MAO inhibitors do since the majority of MAO in the gut is type A. Moclobemide has been used to treat depression and may even be a chop-chop reversible MAO type A drug with a reduced propensity to trigger the cheese reaction [15].

(**d) Na/ K-ATPase—cardiac glycosides**

Sodium/potassium-activated nucleoside triphosphatase (Na/K-ATPase, or the Na/K pump), a membrane-bound protein responsible for the majority of the transport of atomic number 19 into cells and metallic element out of them, is inhibited by viscus glycosides like digitalis glycoside, digitoxin, and ouabain. This maintains the usual high transmembrane gradients of those ions. The beneficial inotropic and chronotropic effects of viscus glycosides are thought to be mediated by this inhibition, most likely by an increase in metallic element concentrations inside viscus cells.

(e) Phosphoinositide—lithium

By inhibiting one in every of the enzymes within the phosphoinositide second traveler system, metallic element alters its turnover. However, If typically, this can be the mechanism by which that metallic element exerts its therapeutic benefits in the therapy of manic-depressive illness, it is unknown [15].

(f) Phosphodiesterase—xanthine, milrinone, sildenafil

By inhibiting one in every of the enzymes within the phosphoinositide second traveler pathway, metallic element alters it. phosphodiesterase area unit enzymes that degrade cyclic AMP, a second traveler in receptor-mediated activities. completely different isoforms of phosphodiesterase occur in distinct tissues. Bronchodilation is caused by Slo-Bid and alternative xanthine obstruction phosphodiesterase inside the respiratory organ. However, as a result of the additionally act on purine receptors, this may not be their key of action. Milrinone and connected compounds, like enoximone, inhibit phosphodiesterase sort three and have a favorable inotropic result on the heart; still, they increase mortality in failure and will be used just for short periods of your time. metallic element modifies the phosphoinositide second traveler pathway by obstruction one in every of its enzymes. phosphodiesterase area unit enzymes that breakdown cyclic AMP, that functions as a second traveler in receptor-mediated actions. in many tissues, completely different isoforms of phosphodiesterase occur. Slo-Bid and alternative xanthine promote bronchodilation by inhibiting phosphodiesterase inside the lungs. they will additionally operate purine receptors, but this may not be their primary technique of action. Milrinone and similar chemicals, like enoximone, inhibit phosphodiesterase sort three and have a helpful inotropic result on the heart;

still, they increase mortality in failure and will solely be administered for brief periods of your time.

(g) Alternative examples

The following are some other medications that function by inhibiting proteins:
The anticancer drug cytarabine inhibits deoxyribonucleic acid polymerase. Some anti-infective treatments function by inhibiting microorganisms or microorganism enzymes. Some antitumor medications, such imatinib, that inhibit amino acid enzyme and alternative kinases. NRTI and didanosine block the human immunological disorder virus (HIV) enzyme, and oseltamivir and zanamivir inhibit the respiratory illness virus neuraminidase, as examples; the quinolones inhibit the microorganism deoxyribonucleic acid gyrase;• The angiotensin-converting protein (ACE) is inhibited by painkillers and non-steroidal anti-inflammatory drugs (NSAIDs); coumarin anticoagulants, such as anticoagulant drugs, inhibit fat-soluble vitamin epoxide reductase; alternative anticoagulants act as inhibitors of coagulase (factor II; argatroban, bivalirudin, dabigatran); or issue Xa (apixaban, fondaparin)

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

(h) Medications that affect the coagulation system

Enzymes are responsible for clotting and fibrinolysis, and drugs that alter these processes make them more active. Antithrombin III is activated by heparin, which prevents clotting. The plasminogen activators streptokinase, urokinase, alteplase, and anistreplase cause clot lysis. Ancrod, the venom of the Malay pit viper, possesses thrombin-like properties that cause clotting to occur [16].

(i) Cancer chemotherapy

A decrease in the number of leukemic cells caused by the enzyme L-asparaginase has been found to benefit some people with acute lymphoblastic leukaemia [16].].

(j) Other examples

Two such examples of drugs that activate or replace enzymes are pralidoxime, which activates cholinesterase in organophosphorus pesticide poisoning, and danazol and stanozolol, which improve the activity of the Cl esterase inhibitor in persons with hereditary angioedema [16].

- **Drug Action Through Unexpected Side Effects**

(a) Unauthorized substances

- The following instances show how metal-chelating medications can be used to quicken the body's elimination of metals:
- • lead poisoning is treated with calcium sodium edetate (ethylene diamine tetra-acetate, or EDTA), which chelates many divalent and trivalent metals; dimercaprol chelates some heavy metals and is used to treat mercury poisoning.
- deferoxamine chelates iron and is used to treat iron toxicity as well as iron overload caused by frequent blood transfusions (for example, in thalassemia);

• Hepatolenticular degeneration (Wilson's disease), which results in copper deposition in the brain's basal ganglia

due to a lack of the copper-binding protein caeruloplasmin, is treated with penicillamine because it chelates copper. It is also used to chelate cystine to prevent renal damage in cystinuria.

(b) Olfactory diuretics

Mannose is linked to mannitol, a hexahydric alcohol that is an isomer of sorbitol. Although it is easily filtered at the renal glomerulus, the renal tubules can only partially reabsorb it. It increases the amount of urine by absorbing water and raising the concentration of osmotically active particles in the tubular fluid. No extra pharmacological effects are present. In the past, mannitol has been used to treat acute poisoning and cerebral oedema by inducing diuresis. In patients with shock, it has been used to restore renal tubular function and urine production. Urea has been used to treat cerebral oedema and functions similarly to mannitol [17].

(c) Analogs of hormones

Drugs that imitate hormones can have effects that are similar to those of their real-life counterparts. Afamelanotide, an analogue of melanocyte-stimulating hormone, has been used to treat erythropoietic protoporphyria, for instance. Chronic renal insufficiency anemia is treated using epoetins, which are synthetic versions of the hormone erythropoietin [17].

(d) Volatile anesthetics in general

These substances lack recognizable molecular characteristics. They include both non-halogenated chemicals (such as nitrous oxide and cyclopropane) and halogenated hydrocarbons (such as halothane, desflurane, enflurane, and trichloroethylene), which have similar effects on the brain. This class of compounds is difficult to incorporate into the conventional pharmacological action models. It is widely believed that their primary effects are on the lipid matrix of biological membranes, which alters the membrane's biophysical properties and causes alterations in ion fluxes or other processes vital to the normal functioning of neuronal excitability [17].

(e) Alternatives to pharmaceuticals

Despite being a pharmacologically arbitrary subdivision, this one has therapeutic value. The best examples are intramuscular injections of hydroxocobalamin (vitamin B12) to treat vitamin B12 deficiency, particularly that which is linked to pernicious anaemia, and oral and parenteral administration of ferrous salts to treat anaemia brought on by iron deficiency. the substances that are employed to make up for shortages. The use of hormones as replacement therapy (for instance, the use of thyroxine to replace naturally occurring thyroid hormone in hypothyroidism) could theoretically fall under this heading, but it is best classified under drugs that directly act on receptors, as hormones do. Similar to this, the substitution of clotting factors, such as factor VIII in haemophilia, belongs to the class of therapies involving direct enzymatic action [16].

VII. DESIRED ACTIVITY

The major reason why a medicine has the desired effect is because one of the following was successfully targeted:

cellular membrane disruption, chemical reactions with aftereffects, interactions with enzyme proteins, structural proteins, carrier proteins, interactions with ion channels, and interactions with structural proteins.

- Ligand-receptor binding:
- Receptors for neuromodulators, neurotransmitters, and hormones

It was often believed that general anesthetics affected Na+ influx by causing disruptions to neuronal membranes. Antacids and chelating agents interact chemically in the body. A technique for changing the synthesis or metabolism of necessary endogenous chemicals is enzyme-substrate binding. For instance, aspirin permanently inhibits the cyclooxygenase enzyme prostaglandin synthetase, avoiding an inflammatory reaction. The structural protein tubulin is inhibited by the gout drug colchicine, while the carrier molecule Na-K-ATPase pump is inhibited by the heart failure drug digitalis. The broadest category of drugs operate as ligands by attaching to receptors that control cellular processes. Drugs may cause their typical activity (agonist), an action that is inhibited (antagonist), or even the opposite action (inverse agonist) when they bind to receptors [16].

In theory, a pharmacologist would aim for a target plasma concentration of the drug to produce the appropriate level of reaction. In reality, a number of factors affect this goal. Pharmacokinetic factors influence peak concentrations, and because of metabolic breakdown and excretory clearance, concentrations cannot be kept constant precisely. Genetic factors that affect metabolism or pharmacological action may exist, and a patient's current condition may also have an impact on the recommended dose

VIII. UNWANTED RESULT

A drug's undesirable side effects can include: • An elevated risk of cell mutation (carcinogenic activity); • A number of concurrent, diverse actions that may be harmful.
• Conversation (additive, multiplicative, or metabolic)
• Inflicted bodily harm or anomalous, long-lasting conditions [17]

Treatment window

The therapeutic window is the range of dosages between the one that has an impact (effective dose) and the one that has more unintended side effects than intended side effects. For instance, medication with a limited pharmacological window needs to be provided carefully and under control, such as by regularly checking the drug's blood concentration, as it is prone to losing its effectiveness or having undesirable effects [18].

Action's duration

The period of time that a drug is effective is measured by its duration of action. The time it takes for plasma and target compartments to equilibrate, as well as the drug's off-rate from its biological target, all affect how long an effect lasts [19].

IX. RECEPTORS SELECTIVITY

The name of a receptor is determined by its main endogenous agonist (e.g. adrenergic, serotoninergic, opioid). Following that, they are often "sub-typed" according to whether they favor agonists or antagonists. The ratio of the EC50 of the dose-response curve at the two separate receptor subtypes determines agonist selectivity. For example, -adrenoceptors may be divided into two types based on their response to the endogenous agonist, noradrenaline. The concentration necessary to generate bronchodilation (through 2 adrenoceptors) is 10 times that required to cause tachycardia (via 1 adrenoceptor). Receptor subtypes may also be identified by the differential efficiency of medications that counteract the effects of their full agonist, as evaluated by the relative shift of the agonist dose-response curves obtained by a single dosage of antagonist influencing responses mediated by the two receptors. It is critical for prescribers to understand that selectivity for a receptor subtype is merely a relative term (i.e., selectivity does not equate with specificity) [20].

When taken in sufficient doses, drugs that are assumed to be "selective" for one receptor subtype can nonetheless have a significant impact on other subtypes. This is particularly true if one receptor subtype activates the advantageous effects while a different receptor subtype activates the unfavorable effects. Examples include "cardioselectivity" -adrenoceptor blocking medications, which have anti-anginal effects on the heart (1) but can cause bronchospasm in the lungs (2) and are therefore strictly forbidden in asthmatic patients. Selectivity is useful in clinical practice only when the ratio of the drug's effect at the two receptor sites is greater than 100. It is challenging to predict pharmaceutical dosages that will take advantage of subtype activity differences when selectivity is low. [20]

X. EFFICACY AND POTANCY

When all available receptors or binding sites are occupied, a drug's "efficacy" relates to how much of a reaction it may cause (i.e. Emax on the dose–response curve). A full agonist has the best effectiveness when comparing drugs that target the same receptor and may elicit the most response that the receptor is capable of delivering. A partial agonist at the same receptor will be less effective even when all receptor sites are filled. Comparing the outcomes of drugs that target the same receptor is only one way to measure effectiveness. Comparing drugs with the same therapeutic effects on a biological system but that do so using different pharmacological mechanisms (such as loop and thiazide) is known as evaluating their therapeutic effectiveness.

The potency of a medication is inversely correlated with its affinity for the receptor (i.e. how readily the drug-receptor complex is formed). The difference in potency can be easily overcome by giving the less potent agent in larger dosages; less potent therapies can be just as effective as more potent ones. This is shown by the various suggested dosage ranges of drugs acting on the same drug target (e.g. H2 antagonists, ACE inhibitors).

It may seem logical to choose the drug with the highest therapeutic efficacy from a group of identical medications when choosing a medication with equivalent positive effects (such as analgesia). The most beneficial medication, however, might not always be the best option because the same mechanism of action that produces therapeutic benefits may also result in dose-limiting negative effects (e.g., opioids, 1-adrenoceptor blocking therapies). When a single activity has both positive and negative effects, it is possible to lessen the latter by progressively increasing (titrating) the dosage. It can be challenging to titrate to the right amount while avoiding side effects, though, because some drugs have a steeper dosage-response curve [21].

Rarely is a drug chosen over a group of medications with comparable effective therapeutic effects based on its potency. This is because any differences in potency can be corrected by simply giving higher dosages. Changes in dosage can be made to address differences in relative potency, but it's crucial to remember that most pharmacological adverse effects are also dose-related. Potency may be important if these happen

through a mechanism other than the receptor-ligand interaction that causes the beneficial effect (because only the more potent medicine would be active at levels that minimize unfavorable side effects) [21].

These factors make it so that more potency or efficacy does not necessarily suggest that one medicine is better than another. The therapeutic index, convenience of administration for the patient, duration of effect (i.e., the number of doses needed each day), cost, and the overall adverse effect profile are other crucial factors to consider when assessing the relative benefits of drugs for a patient [21].

XI. INTRODUCTION TO THE DOSE RESPONSES RELATIONSHIP, SECTION

A sigmoidal dose-response curve is created when the relationship between drug dose (X-axis) and drug response (Y-axis) is displayed on a base 10 logarithmic scale. Because it expands the dosage scale where medication response is changing quickly and compresses the scale at higher dosages where major changes have little impact on response, this method is more illuminating than a linear plot. Changes in heart rate, blood pressure, gastric pH, blood glucose, as well as more subtle phenomena like enzyme activity, buildup of an intracellular second messenger, membrane potential, hormone secretion, or muscle contraction, might all be plotted as clinical reactions [22].

Progressive dosage increases cause medication effects to intensify, but only within a very small range of total concentration; further dosage increases (or increases in concentration) outside of this range have little additional effect. This link has practical significance because just increasing a patient's medication dosage could not have any further therapeutic effects and might potentially have the opposite effect. The ED50 is the dosage (or concentration) that yields half of the maximal response on the curve, or Emax (Emax/2) (or EC50). The log dose-response curve's straight-line region, which corresponds to 20–80% of Emax, can be thought of as the effective dose range. The highest dosage of a medicine that can be tolerated is known as the maximum tolerated dose.

Because higher agonist concentrations are needed to achieve a given percentage receptor occupancy when an agonist and competitive antagonist are coupled, the agonist dose-response curve shifts to the right (and therefore effect). When a competitive antagonist is present in increasing dosages, the agonist's dose-response curves are gradually shifted to the right. Nevertheless, the effects of a reversible competitive antagonist can always be neutralized by giving the agonist in sufficiently high doses (i.e. it is surmountable). There are numerous competitive antagonists that have therapeutic benefits (e.g. atenolol, naloxone, atropine, cimetidine). Non-competitive antagonists prevent the action of an agonist by means other than by directly competing with it for receptor binding (e.g. by affecting the secondary messenger system). Due to this, even at very high agonist concentrations, the maximum response is impossible to obtain. In addition to shifting the agonist dose-response curve to the right at a specific dosage, non-competitive antagonists can reduce Emax. Antagonism between irreversible antagonists, a type of non-competitive antagonist, persists long after the antagonist is vanquished. Two typical examples are omeprazole and aspirin. This kind of antagonistic relationship only ends when new proteins or enzymes are produced. This explains why aspirin, even when used infrequently, is effective at preventing cardiovascular events [23].

Due to a multitude of factors, including differences in receptor number and structure, receptor-coupling mechanisms, and physiological changes brought on by genetic, ageing, and health inequities, the dose-response relationship to the same medicine differs between individuals. For instance, the action of the loop diuretic furosemide is typically significantly diminished at a given dose in those with renal impairment. Due to differences in handling, the same pharmaceutical dose does not produce the same tissue drug concentrations in all individuals (e.g. metabolism, excretion). The majority of the inter-individual variation in pharmaceutical response seen in clinical practice is actually explained by pharmacokinetic variance [23].

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