**Book Chapter**

**Introduction to Pharmacology and Pharmacodynamics**

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**A B S T R A C T**

In this review, four fundamental pharmacodynamics principles are discussed, including drug receptor interaction, molecular mechanisms underlying pharmacological action, and dosing guidelines. On the basis of pharmacodynamics. It's crucial to quantify the time course of pharmacodynamics responses in relation to plasma drug concentrations in order to comprehend and anticipate the pharmacologic behavior of medications. If at all possible, the choice of an acceptable model should be made based on the drug's method of action as well as other elements of biological reality. In addition, calculating inaccessible Pharmacodynamics stages and parameters can be a benefit of mechanism-based physiologic models. Drug side effects that are reversible can be roughly divided into direct and indirect reactions.

**Keywords:** pharmacodynamics, indirect response models

**1. Introduction**

Pharmacodynamics is the study of a drug's molecular, biochemical, and physiological effects or actions. Its root words are "Pharmakon," which is Greek for "drug," and "Dynamikos," which is Greek for "power." All drugs function by engaging in molecular interactions with biological targets or structures that change the functionality of the target molecule in relation to forthcoming intermolecular interactions[1]. These interactions include receptor binding, chemical interactions, and effects after the receptor. One of the essential tenets of pharmacology is that for a pharmacological response to occur, drug molecules must chemically interact with one or more cell components. In other words, the function of these fundamental biological molecules must be altered by the chemical interactions between drug molecules and them[2]. The likelihood of a drug molecule interacting with a particular class of cellular molecule would be incredibly low if the drug molecules were just spread at random because there are obviously far more molecules in an organism than there are medication molecules. The non-uniform distribution of the drug molecule inside the body or tissue is therefore required for pharmacological effects, which is the same as saying that drug molecules must be 'bound' to certain components of cells and tissues in order to generate an effect[3].

*1.1 Protein targets for drug action*

Receptors, enzymes, carrier molecules (transporters), and ion channels, the four major subtypes of regulatory proteins, are usually chosen as the main therapeutic targets. Many drugs also attach to tissue proteins other than their primary targets, such as plasma proteins, with no obvious physiological effect. The generalization that most drugs have an impact on one or more of the four protein types outlined above is still a good place to start. These crucial binding sites are sometimes referred to as "drug targets." The process through which a drug molecule interacts with its target to produce a physiological response is the principal subject of pharmacological investigation. Drugs' principal targets are protein molecules. Even general anesthetics, which were originally thought to interact with membrane lipid, now appear to interact with membrane proteins in the majority of cases. There are several antibacterial, anticancer, mutagenic, and carcinogenic chemicals that interact with DNA rather than proteins, proving that every rule has an exception. In the same way that rat poison is poisonous to osteoclasts, bisphosphonates, which are used to treat osteoporosis, bind to calcium salts in the bone matrix. Nucleic acids, proteins, and antibodies are examples of the biopharmaceutical drugs of the new generation that are an exception. To coordinate the activity of their cells and organs, all multicellular organisms require a system of chemical communication, and receptors are an essential component of this system. Without them, we wouldn't be able to function. A few essential traits of receptors are illustrated by the impact of adrenaline (epinephrine) on the heart. The first protein to which adrenaline binds is the 1 adrenoceptor, which serves as a recognition site for adrenaline and other catecholamines. As it binds to the receptor, the heartbeat intensifies and accelerates, setting off a series of actions. When no adrenaline is available, the receptor frequently operates silently. The drug-target interaction that takes place downstream causes effects, which can be measured using biochemical or clinical techniques. Examples of this include the inhibition of platelet aggregation after aspirin administration, the lowering of blood pressure after ACE inhibitors delivery, and the role of insulin in lowering blood glucose. The administration of the drugs in the aforementioned examples may seem obvious, but it's important to keep in mind that the pharmacodynamic effects of these medications are what practitioners use to lower the risks of cerebrovascular accident, myocardial infarction, renal complications, and eye complications rather than to inhibit platelet aggregation, lower blood pressure, or lower blood glucose [4]. The patient must always come first for medical practitioners, not the symptom or the lab result. Pharmacodynamics and pharmacokinetics are the two subfields of pharmacology, with pharmacodynamics concentrating on how medications interact with organisms and pharmacokinetics investigating this interaction.

*1.2 Pharmacodynamics actions*

The following are examples of Pharmacodynamics actions:

1. Stimulating activity by directly blocking a receptor and its aftereffects.
2. Direct receptor inhibition-induced depressive activity and associated after-effects.
3. Direct chemical responses (helpful in therapy as well as an undesirable occurrence).
4. Antagonistic or inhibiting a receptor by binding to it but not activating it.
5. Stabilizing action, when the drug appears to operate neither as an agonist nor antagonist.
6. Any one of these elements has the potential to be both therapeutic and to cause an undesirable outcome.

**Receptor interactions with drugs:**

It may or may not happen that a drug molecule occupies a receptor before activating it. The term "activation" refers to the effect that the connected chemical has on the receptor, which alters how the cell behaves and results in a tissue reaction. Binding and activation are two distinct steps that take place when an agonist causes the receptor-mediated response. If a chemical binds to a receptor without activating it in order to prevent the binding of the agonist, that substance is referred to as a receptor antagonist. The frequency with which a drug binds to receptors is determined by its affinity, whereas the likelihood that the medication will activate the receptor once bound is determined by its efficacy. High potency drugs typically bind to receptors with high affinity, taking up a sizable fraction of the receptors even at low concentrations. In contrast to antagonists, who in the simplest scenario have no efficacy, agonists also have high efficacy. To distinguish them from full agonists, whose efficacy is sufficient to elicit a maximal tissue response, drugs with intermediate degrees of efficacy are known as partial agonists. Even when 100% of the receptors are occupied, the tissue response is still submaximal. Although these ideas plainly oversimplify chemical events, they still serve as a valuable framework for describing medication effects.

*1.3 Partial agonists and the concept of efficacy*

Drugs have only been thought of as either agonists or antagonists thus far. Agonists do not activate the receptor in any way when they occupy it. The efficacy of a pharmacological molecule, or its capacity to activate the receptor, is actually a graded feature as opposed to an all-or-nothing one. The biggest response that can be achieved varies from drug to drug when a series of chemically related agonist medicines that act on the same receptors is tested on a specific biological system. Some substances (referred to as complete agonists) can trigger the tissue's maximum reaction, while others (known as partial agonists) can only trigger a submaximal response.

**Some important points to be remember:** Drugs acting on receptors may be agonists or antagonists.

* While antagonists bind to receptors without causing changes in cell function, agonists start such changes and result in consequences of various kinds.
* The ability of an agonist to cause changes that result in consequences depends on two factors: effectiveness and affinity (i.e., the propensity to bind to receptors). Efficacy for antagonists is nil.
* Partial agonists, which can only cause submaximal effects, have intermediate efficacy compared to full agonists, which can produce maximal effects.
* In accordance with the two-state concept, efficacy reflects the substance's relative affinity for the receptor's resting and active states. In contrast to antagonists, agonists display selectivity for the active state. Although useful, this model is unable to capture the complexity of agonist activity.
* Inverse agonists exhibit selectivity for the receptor's resting state; however, this is only significant when the receptors exhibit constitutive activity.
* Allosteric modulators can change the action of an agonist by attaching to locations on the receptor other than the agonist binding site.

**2. Molecular basis of drug action:**

Drugs interact with biological targets to produce their desired effects, but the speed of action depends on the target's metabolic pathway and mechanism. Effect types include direct, indirect, immediate, and delayed effects. Direct effects are frequently the outcome of drug interactions with a receptor or enzyme that is crucial to the effect's route. Beta-blockers stop smooth muscle cell receptors from directly regulating cAMP levels in the vasculature. Drugs have indirect effects when they interact with receptors and proteins of other biologic structures that are far removed from the biochemical reaction that ultimately causes the drug impact. Nuclear transcription factors that the cell's cytoplasm binds to go to the nucleus and stop the transcription of DNA into mRNA that produces different inflammatory proteins. Normal order is for immediate effects to follow direct pharmacological actions. Succinylcholine, which is composed of two acetylcholine (ACh) molecules joined end to end by their acetyl groups, interacts with the nicotinic acetylcholine receptor (nAChR) on skeletal muscle cells to impede neuromuscular transmission[5]. As a result of the channel remaining open, the membrane depolarizes, an action potential is generated, muscles contract, and 60 seconds after delivery, paralysis sets in. Before any delayed effects, there may be immediate side effects from the medicine. Patients with acute myeloid leukemia who receive chemotherapy medicines such cytosine arabinoside, which block DNA synthesis, develop bone marrow suppression days after treatment.

*2.1 Receptors*

The numerous hormones, transmitters, and other mediators discussed in Section 2 of this book serve as chemical messengers, serving as the sensing elements in a network of chemical communications that coordinates the function and responses of all the various cells in the body. Many drugs with therapeutic effect work as agonists or antagonists on known endogenous mediator receptors. The bulk of the time, the endogenous mediator was identified years before the receptor was pharmacologically and biochemically defined. For some receptors, like the cannabinoid and opioid receptors, endogenous mediators were subsequently discovered; however, the mediator, if any, is still unknown for other receptors, known as orphan receptors (see later). The host defense system additionally employs a class of receptors known as "Toll" receptors, which are adept at recognizing fragments of "foreign" bacteria and other invasive species.

*2.2 Ion channels*

Ion channels are essentially gateways in the cell membrane that only allow certain ions to pass through. They can be stimulated to open or close in a variety of ways. There are two important types: ligand- and voltage-gated channels. The former is accurately characterized as receptors since they only open when one or more agonist molecules are attached and agonist binding is necessary for their activation. Voltage-gated channels are opened by alterations in the transmembrane potential as opposed to agonist binding. Medication side effects can generally be classified into the following categories: 1. The drug molecule physically blocks the channel by attaching to the channel protein, either at the ligand-binding (orthostatic) site of ligand-gated channels or at alternative (allosteric) locations, as shown by the action of local anesthetics on the voltage-gated sodium channel. A drug that binds to allosteric sites on the channel protein and changes channel gating is benzodiazepines. These drugs bind to a location on the GABAA receptor-chloride channel complex (a ligand-gated channel) that is distinct from the GABA binding site, assisting the inhibitory neurotransmitter GABA in opening the channel. Dihydropyridine-type vasodilators that prevent L-type calcium channels from opening.

*2.3 Enzymes*

Numerous drugs target enzymes. For example, captopril inhibits angiotensin-converting enzyme; in other cases, the binding is irreversible and non-competitive (for example, aspirin inhibits cyclooxygenase). In many cases, the drug molecule is an analogue of the enzyme's substrate that inhibits it competitively. Drugs may also act as "false substrates," in which case the drug molecule undergoes a chemical transformation to produce an abnormal byproduct that obstructs the normal metabolic pathway. For instance, fluorouracil, an anticancer drug, cannot be converted into thymidylate, which prevents DNA synthesis, stops cell division, and replaces uracil as an intermediary in purine biosynthesis. It's also important to keep in mind that some drugs must undergo enzymatic degradation in order to turn from an inactive form, known as a prodrug, to an active form (for example, esterases convert the drug enalapril into enalaprilate, which inhibits the angiotensin-converting enzyme) [6]. In addition, drug toxicity frequently results from the enzymatic conversion of the drug molecule into a reactive metabolite. The liver is harmed in this manner by paracetamol. This undesirable side effect has a large practical impact despite having little to do with the drug's intended function.

*2.4 Transporters*

Ions and small polar chemical molecules often pass across cell membranes either through channels or with the help of a transport protein because penetrating molecules are frequently too lipid-soluble to do soon their own. There are numerous such transporters; examples of particular pharmacological significance include those in charge of transporting ions and a variety of organic molecules through the blood-brain barrier, intestinal epithelium, and renal tubule, moving Na+ and Ca2+ out of cells, transporting drug molecules, and more. Transporters will occur frequently in later chapters. The hydrolysis of ATP frequently provides the energy for the movement of molecules across their electrochemical gradient.

Because they feature a characteristic ATP binding site, these transport proteins are referred to as ABC (ATP-Binding Cassette) transporters. Two notable examples are the sodium pump (Na+-K+-ATPase) and multidrug resistance (MDR) transporters, which release fatal drugs from malignant and microbial cells and confer resistance to these therapeutic medicines. As a result of the coupling between the transport of organic molecules and the transport of ions (typically Na+), either in the same direction (symport) or the opposite direction (antiport), other situations, such as the neurotransmitter transporters, rely on the electrochemical gradient for Na+ produced by the ATP-driven sodium pump. Cocaine, for example, blocks the uptake of monoamine neurotransmitters into nerve terminals because it has a recognition site that makes the carrier proteins specialized for a certain penetrating species. Drugs that disrupt the transport mechanism can also target these recognition sites. The significance of transporters as a source of individual variation in the pharmacokinetic characteristics of many medications is becoming more widely recognized.

**3. Dosing Principles-Based Upon Pharmacodynamics**

Dose-receptor connections, or the interactions between a drug's concentration and its effect, are the focus of pharmacodynamics. As an illustration, we can look at drug-receptor interactions using the following formula:

In this equation, L stands for the ligand, or drug concentration, R for the receptor concentrations, and LR for the concentrations of the ligand-receptor complex.

Additional pharmacodynamics ideas include:

Kd: Both the drug's concentration at the receptor site and how strongly it binds to its target determine the pharmacologic response. Kd is a metric for how firmly a medication binds to a receptor. The ratio of the drug's attachment and dissociation rate constants to and from the receptors is known as Kd. At equilibrium, the rate of creation of the receptor-drug complex equals the rate of dissociation into the receptor and drug components. An equilibrium or affinity constant (1/Kd) can be determined by measuring the reaction rate constants[7,8]. The higher the antibody's affinity for its target, the lower the Kd value should be. For the beta-2 receptor, albuterol, for instance, has a Kd of 100 nanomolar (nM).

*3.1 Occupancy of Receptors*

According to the rule of mass action, theP pharmacodynamics response increases when more receptors are occupied by the drug, albeit not all receptors must be engaged to achieve the maximum response. This idea, known as the concept of spare receptors, frequently refers to steroid receptors, catecholamine receptors, and the muscarinic and nicotinic acetylcholine receptors.

*3.2 Receptor Up- and Downregulation*

A prolonged antagonist exposure usually results in receptor upregulation, or an increased number of receptors, whereas a chronic agonist exposure usually results in receptor downregulation, or a lower number of receptors. Without changing the number of receptors on the cell membrane, additional mechanisms involving the modification of downstream receptor signalling may also be implicated in up- or downmodulation. As a result of prolonged insulin exposure, the insulin receptor is downregulated. Increased hormone binding causes receptor internalisation and degradation, which leads to a steady decrease in the number of insulin surface receptors[9]. Despite nicotine being an agonist, the nicotine receptor is an exception to the rule since it shows upregulation in receptor numbers after prolonged treatment, which explains some of the differences.

*3.3 Clinical Significance*

The concepts of Kd, receptor occupancy, and up/downregulation can be used to explain a variety of dosing-related problems. Long-term opioid use typically results in tolerance, when the effects of the drug appear to fade with additional doses. Arrestins are intracellular proteins that are stimulated to be produced when opioid receptors are activated[10]. Arrestins attach to the opioid receptor's intracellular region, suppress G-protein signalling, and cause receptor endocytosis. Less "signalling" or tolerance arises from this. One of the various processes that results in receptor down-regulation and receptor tolerance is arrestin activity[11]. It should go without saying that the objective of pharmacodynamics in the context of pharmacological therapy is to exert beneficial effects at the lowest dose necessary to generate the greatest therapeutic benefit while minimising the pharmacodynamics that results in an adverse event[12]. All members of the interprofessional healthcare team who prescribe, dose, dispense, or deliver pharmacological therapy must have a working knowledge of Pharmacodynamics and pharmacokinetic principles. It goes without saying that knowledge must match the practitioner's clinical role.

*3.3 Enhancement of the healthcare provider’s outcome*

However, pharmacologic therapy properly involves an inter-professional team that includes all clinicians who order or prescribe medications, pharmacists, who are without a doubt the subject matter experts regarding pharmacodynamics and their application in drug therapy; clinicians should use them as a valuable resource because of this specialisation, and nurses, who in addition to the pharmacists can counsel the patient about their medications, administer them in a safe manner, and monitor their Patient outcomes can be improved while adverse events are reduced by using an inter-professional team approach to medication that incorporates the proper Pharmacodynamics understanding.

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