PHARMACODYNAMICS

Abstract

The field of pharmacodynamics studies how a ligand (Hormone or a Neurotransmitter), binds to its receptor to produce a pharmacological response. It's a term used to describe the effects of a drug on the body, including the biochemical and physiologic effects that influence the interaction of the drug with the receptor. The integration of actions in molecules into an effect on the organism is addressed in this chapter. It is important to describe the effects of a drug.

Keywords: Pharmacodynamics, ligand-receptor binding ,pharmacological response, interaction

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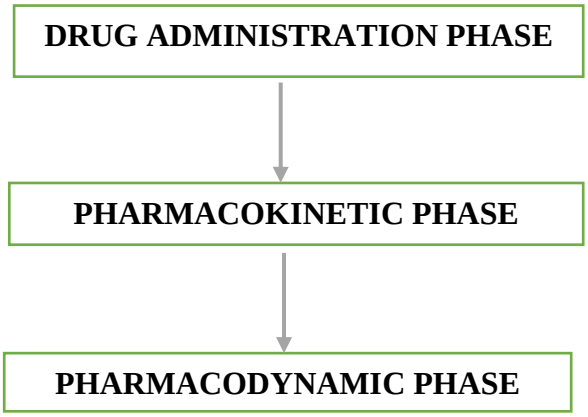
I. INTRODUCTION

Successful pharmacotherapy depends on the impact of these variables as well as how effectively the body responds to drugs at specific target locations. The process of drug delivery involves three phases, namely the drug administration phase, the pharmacokinetic phase and the pharmacodynamic phase. In this chapter, we will be discussing the third phase which deals with drugs producing a change or an effect on a specific target. This phase involves the interaction of a drug with its specific target, called a receptor.



II. PHARMACOKINETICS AND PHARMACODYNAMICS

There are two phases of drug action. (Fig.1). The pharmacokinetic phase is the rate of movement of drugs within the biological system, It explains how a body can handle a drug during the process of adsorption, distribution, metabolism and elimination; the pharmacodynamic phase involves the study of what the drug does in the body, the drug interacts with the receptor to produce a pharmacological effect.

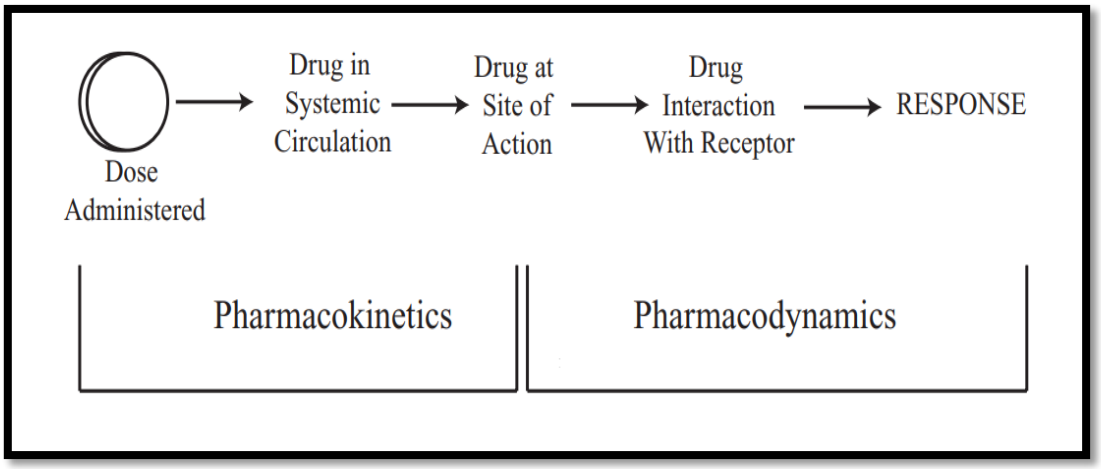


Figure: 1

III. FUNDAMENTALS OF DRUG ACTION

The alteration of the biochemical or physiological process of tissues of organisms by any chemical agent which is intended for diagnostic, preventive and therapeutic purposes is

called a "drug". The term drug is derived from the French term "Drogue" which means a medicament. Sources of drugs can be plants, animals, synthetic sources, minerals and genetic means.

A drug molecule is expected to exhibit its mechanism of action on the target site. There are principles based on which the drug elicits an action that can be classified broadly into the following types,

1. **Activation:** The drug molecule stimulates the process or selectively accelerates the process by binding to the target site. Example: Caffeine causes CNS stimulation and increased alertness.

2. **Inhibition:** Drug molecule exhibiting its action by inhibiting the process or selectively deaccelerating the process by binding to the target site. Example: Aspirin inhibits cyclooxygenase, thereby inhibiting the formation of prostaglandins.

3. **Complexation:** Drug molecule exhibiting its action by making a complex, thereby making it inactive by sequestration. Example: Deferoximine chelates ion.

4. **Neutralization:** Drug molecule binding to the target site and neutralizing the action of the existing molecule directly through a chemical reaction. Example: Antacids

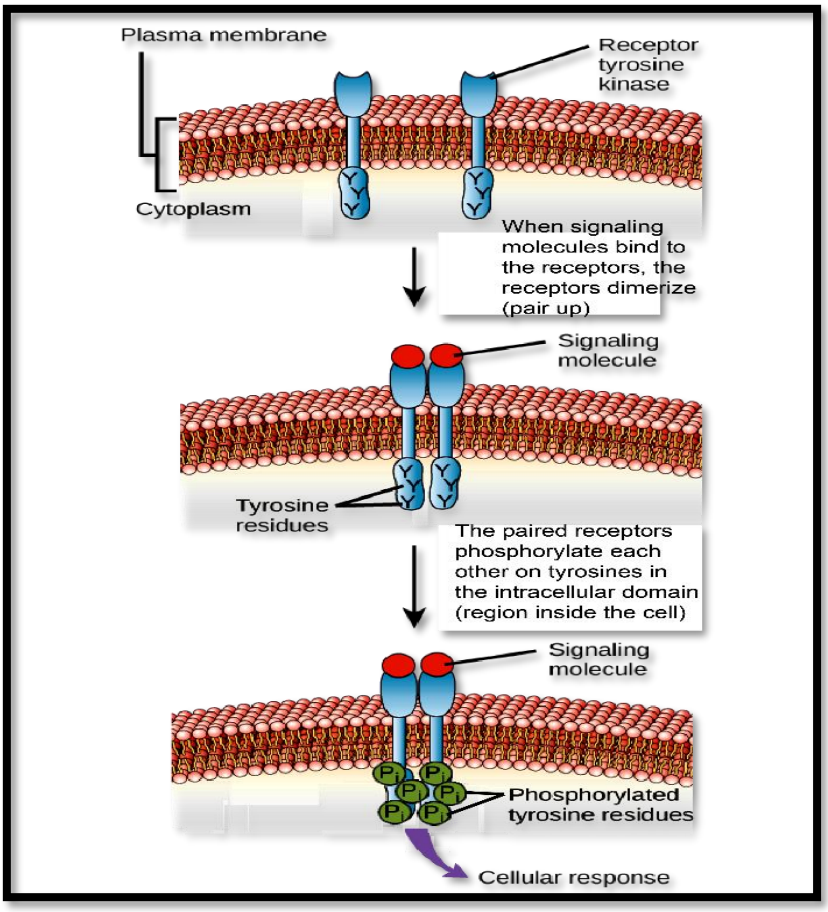


Figure 2: Recognition of a Drug by a Receptor

IV. FACTORS INFLUENCING THE EFFECTIVENESS OF DRUG THERAPY

The concentration of administered drug
Metabolic rate
Frequency of doses administered
Genetics
Food-Drug interaction
Drug-Drug interaction
Excretion rate
Absorption rate
The half-life of an administered drug
Medical conditions

V. TARGETS OF DRUG ACTION

Most of the drugs produce their significant effects by interacting with target biomolecules. These are usually a functional protein. The principal targets for drug action on mammalian cells can be broadly divided into the following categories:

1. **Receptors** are the most important targets of drug action. Ion channels, enzymes and carrier molecules can also be indirectly activated or inhibited by receptor-mediated actions. Receptors are the sensing elements chemical through chemical communication that coordinates the functions of the body, the chemical messenger can be a hormone or a transmitter substance. Some of the common receptors are biogenic amines, acetylcholine and opiates. The receptors present determine the quantitative relation between drug dosage and pharmacological action and are responsible for the selectivity of drug action. Many drugs function by blocking receptors as antagonists although they do not alter receptor function as agonists do.

2. **Ion channels** can be modulated by drugs in different ways. These channels are opened via a ligand gated channel. Eg. nicotinic receptor are opened by nicotine. Some channels are opened via G-protein .Eg. Beta adrenergic receptor which is activated by calcium channels in the heart.But most of the ion channels are modulated by drugs that directly bind to parts of the channel protein. Example for Ion channels are Na+, K+ and CI-.

3. **Enzymes** are targets for many drugs. Most commonly the drug molecule acts as a substrate analogue which acts as a competitive inhibitor of the enzyme. Competitive inhibition occurs only when there is a similarity in the drug structure and the substrate. In some cases, the inhibition can be irreversible, eg. organophosphorus compounds on AChE, and aspirin on platelet cyclooxygenase.

4. **Transporters** are the carriers that are involved in transporting substrate across the biological membrane. These are carrier proteins with recognition sites which can be targeted for a drug. A few carrier proteins are Na^+/K^+ pump, proton pump and noradrenaline uptake. In addition to these some drugs act on structural proteins, eg. Colchicine on tubulin.

VI. THEROIES IN DRUG- RECEPTOR INTERACTIONS

1. **Occupation theory:** Drugs may act on an independent binding site and activate them, these results in a biological response that is proportional to the drug-receptor complex formed. The intensity of effect is directly proportional to the number of receptors occupied.

2. **Rate theory:** The response of drug is proportional to the receptor-drug complex formed. The rate determines the occupancy of the receptor by the total number of drug per unit time.

3. **Macromolecular theory:** This theory suggests that, when the drug receptor complex is formed, a specific or non-specific type of perturbation will be possible.

4. **Induced-fit theory:** According to the induced fit theory, the binding process of drug produces a mutual moulding of both the ligand and the receptor. Conformational changes occur which is named as the dynamic process. The conformational change is then translated into biological effect.

5. **Activation aggregation theory:** This theory is an extension of macromolecular perturbation theory; it suggests that, at equilibrium receptor will exist in an active state and an inactivated state. Agonist binds to the activated state and antagonist binds to the inactivated state and they shift the equilibrium. Partial agonists bind to both the activated and inactivated state of the receptor.

VII. RECEPTORS AND RECEPTOR-BINDING

Paul Ehrlich, who initiated the concept of 'receptor' at the beginning of this century, he described the drugreceptor interaction as a 'lock and key system'.Majority of the drug receptors are macromolecular proteins which provide both the necessary diversity and specificity of shape and electrical charge. Receptors present in different cellular constituents are specific in size, shape and structure, and allow interaction with specific ligands or substrates. Therefore, specific drugs bind with specific receptors. If the forces that bind the two are weak, the binding will be reversible, but if the forces involved are strong, the binding will be effectively irreversible. Drug-receptor binding is also known as receptor occupancy. Receptor occupancy of a drug is dependent on the affinity of the receptor for the drug which is a function of the structural relationship between the two-the drug and the receptor. The relationship between the ligand concentration and receptor occupancy law of mass action.

The law of mass action states the rate of a chemical reaction is directly proportional to the product of the reactant concentration values.

This means receptor occupancy (%) is directly related to log-concentration of ligand over a wide range. Drug-receptor interactions at different sites in the body are similar, but the transduction mechanisms or the signalling mechanisms by which the drug-receptor occupancy is translated into biological effects are different at different sites. Four such mechanisms have been distinguished, given below in the table.

1. The first three types concern membrane-bound receptors
2. The fourth one concerns cytosolic or nuclear protein receptors.

From the table below it is evident that the time lag between ligand-receptor coupling and response is widely variable depending on the mechanism. The lag period may be in milliseconds, seconds, minutes or even hours or days.

Table 1: Receptor and Receptor Binding

	Ligand-gated channel	**G-protein coupled receptors**	**Tyrosine kinase-linked receptors**	**Intracellular receptors**
Receptor Site	Membrane	Membrane	Membrane	Intracellular
Receptor-Effector Coupling	Direct	G-protein	Direct	via DNA
Effector	Channel	Enzyme /Channel	Tyrosine Kinase	Gene Transcription
Coupling-Response Time Lag	Milliseconds	Seconds	Minutes	Hours/days
Cellular Effects	Hyperpolarization/ Depolarization	Second messenger /Channel modulation	Protein Phosphorylation	Protein synthesis
Examples	n-ACh receptor GABA receptor Glutamate receptor Aspartate receptor	m-Ach receptor Adrenergic receptor 5-HT receptor Polypeptide Hormones	Insulin Growth factors	Corticosteroids Sex hormones Vitamin D Thyroid Hormones

VIII. RECEPTOR GROUPS

A receptor can be defined as a biological macromolecule in the membrane or in a cell to which a drug binds and produces a response. These receptors can be sub-divided into four main groups (Fig.3)

1. Ligand-gated ion channels
2. G protein-coupled receptors
3. Enzyme-linked receptors
4. Intracellular receptors

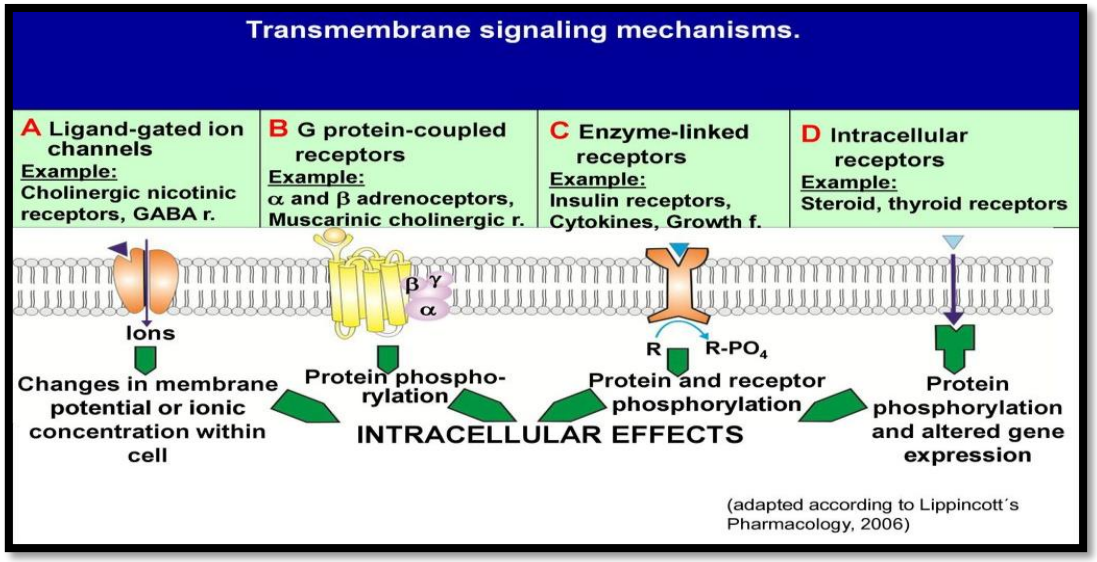


Figure 3: Transmembrane Signalling Mechanisms

1. **Transmembrane ligandgated ion channels:** The drug binding site is located in the extracellular portion of ligand-gated ion channels. This regulates the opening and closing of the pore through which transport across cell membranes takes place. The channel will open only when the receptor is activated. The ions that are transported across this membrane have specific functions in different cells of the body.

2. **G Protein coupled receptors:** The drug binding site is located in the extracellular portion of ligand-gated ion channels and the intracellular portion interacts with the G protein. There are different types of G proteins and they are all composed of 3 sub-units of protein. The α subunit, β ,γ subunits. The responses of these receptors last from several seconds to minutes. The activated effectors produce "second messengers", which further activate other effectors in the cell.

3. **Enzyme-linked receptors:** These receptors are a group of multi-subunit transmembrane proteins that contain either intrinsic enzyme activity on their intracellular domain or associate directly with the intracellular enzyme. When this family of receptors undergoes conformational changes it results in increased intracellular enzyme activity. Response lasts for minutes to hours. For example, growth factors and insulin possess tyrosine residues on themselves and other specific proteins. Phosphorylation acts as a molecular switch because they modify the structure of the target protein. Enzyme-linked receptors are similar to G protein-coupled receptors.

4. **Intracellular receptors:** Intracellular receptors are receptor proteins that are found on the inside of the cell. The ligands are small, hydrophobic molecules; to reach the receptors.Lipid solubility is required for the ligand to diffuse into the cell to interact with the receptor. This receptor can take from hours to days to occur. Other examples for targets of intracellular ligands are structural proteins, ribosomes and enzymes.

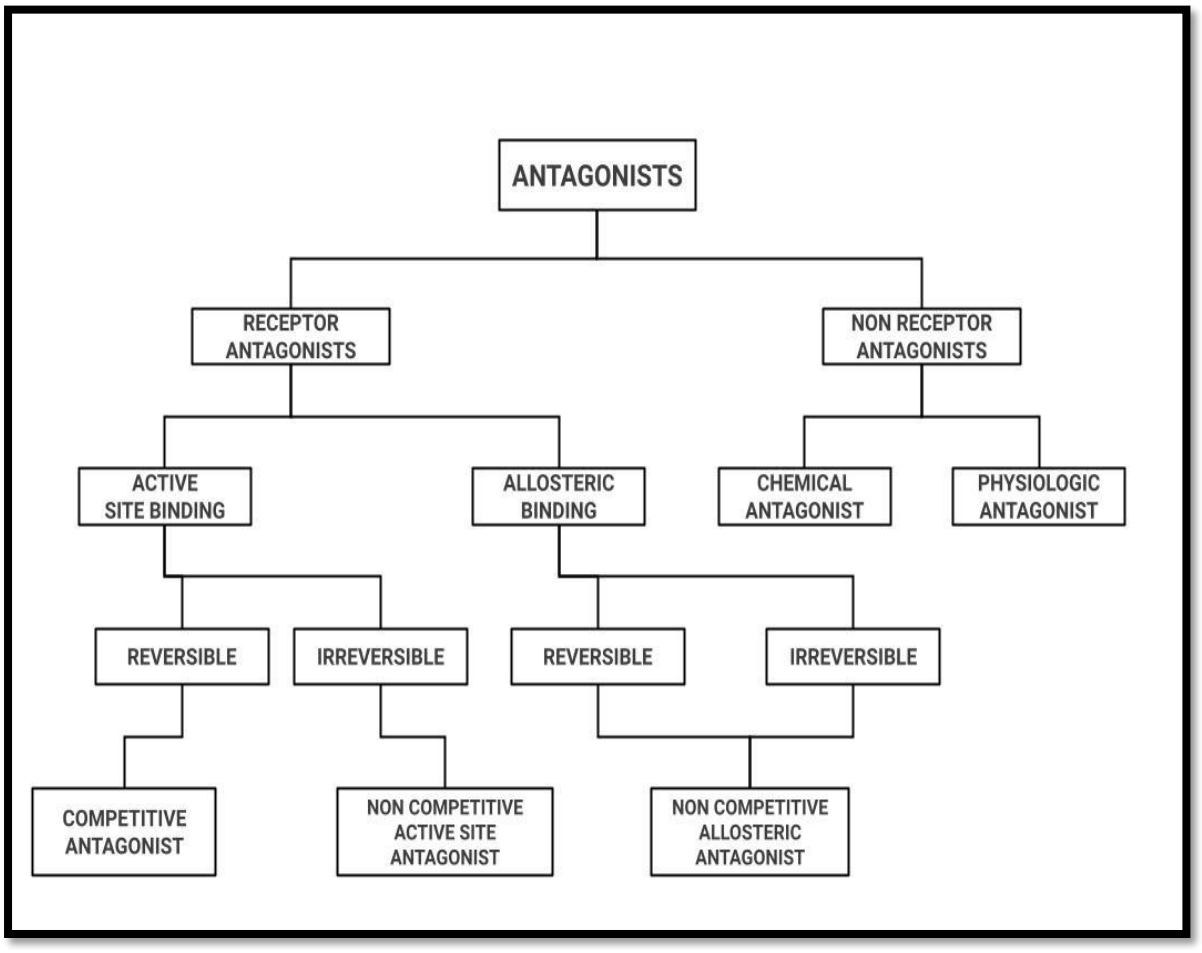
IX. RESPONSE OF DRUG-RECEPTOR INTERACTION

The drug-receptor coupling leads to a number of responses depending upon the nature of the drug molecule.

1. **Agonists:** Drugs resemble the natural transmitter or hormone, may activate the concerned receptor, and result in a response. The capacity of a drug to interact with a receptor is due to its 'affinity', and the capability to produce a response is called its "intrinsic efficacy" or "intrinsic activity". Thus an agonist has affinity as well as an intrinsic activity. Noradrenaline, acetylcholine, histamine, 5-HT and their chemical analogues are all examples of agonists.

2. **Antagonists:** Some drugs because of their structural similarity with the natural ligand of a receptor have an affinity for the receptor and so bind with the receptor. They are however incapable of activating the receptor due to a lack of intrinsic activity (efficacy), and hence there is no response. These drugs compete with the endogenous ligand or exogenous agonists and prevent their receptor occupancy and response. Drugs with affinity without any intrinsic activity and which competitively antagonize the effects of agonists are called pure antagonists. A large number of antagonists are in clinical use, eg. Antiadrenergic, anticholinergics and antihistaminic.

Classification of antagonists based on the binding site



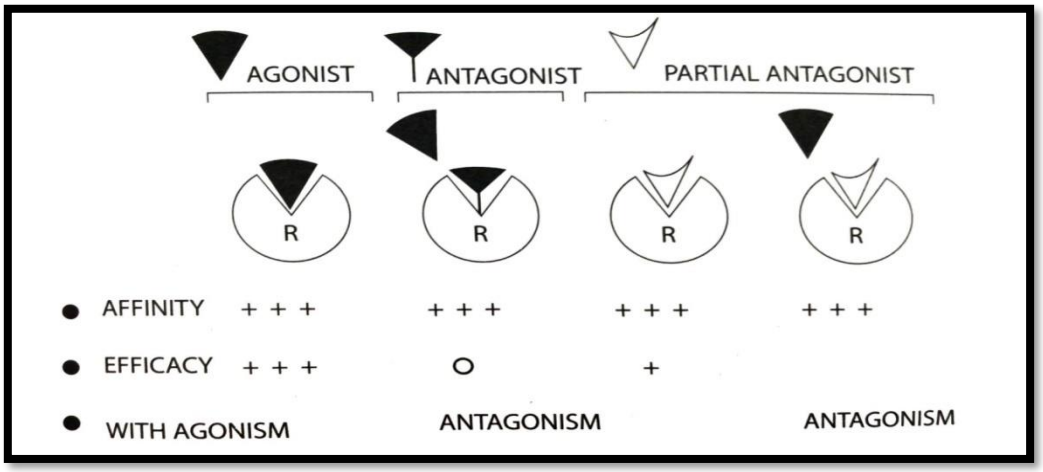


Figure 5: Drug Receptor Interaction

3. **Partial agonists:** Some drugs have both agonist and antagonist actions. They have affinity but very low intrinsic efficacy. They antagonize the effects of a full agonist competitively, but by themselves produce a response that is much lower than that of a full agonist even at full receptor occupancy. A classical example of a partial agonist is saralasin acting on angiotensin II receptors. It has an antihypertensive effect in patients with increased angiotensin II production but raises blood pressure in patients who produce low amounts of angiotensin.

4. **Inverse agonists:** Some drugs produce paradoxical actions, and are specifically opposite to those of the agonists. These are called inverse agonists. β -Carbolines are examples of inverse agonists. These agents, by acting on benzodiazepine receptors will produce anxiety, increase in muscle tone, while the agonist benzodiazepines by binding with the same receptors will produce sedation, anxiolysis, and relaxation of muscles. These types of drugs act by modulating the effects of the neurotransmitter GABA.

X. RELATIONSHIP BETWEEN DOSE-RESPONSE

The effect produced by a drug is dependent on the concentration of the drug at the target site, this is where the drug receptor binding is in equilibrium, it is the relationship between drug response and drug concentration.

Two important drug characteristics are to be considered, The efficacy and potency, These can be determined by graded dose-response curves.

1. **Potency:** It is the amount of drug required to produce an effect to a given intensity. (EC-50) is used to determine potency often. In the given graph, the EC-50 indicate the potency of the drug. (Fig.6) The therapeutic preparations of drugs reflect their potency. the range of drug concentrations that cause from 1% to 99% of maximal response usually spans several orders of magnitude, to graph the complete range of doses ,semilogarithmic plots are being used.

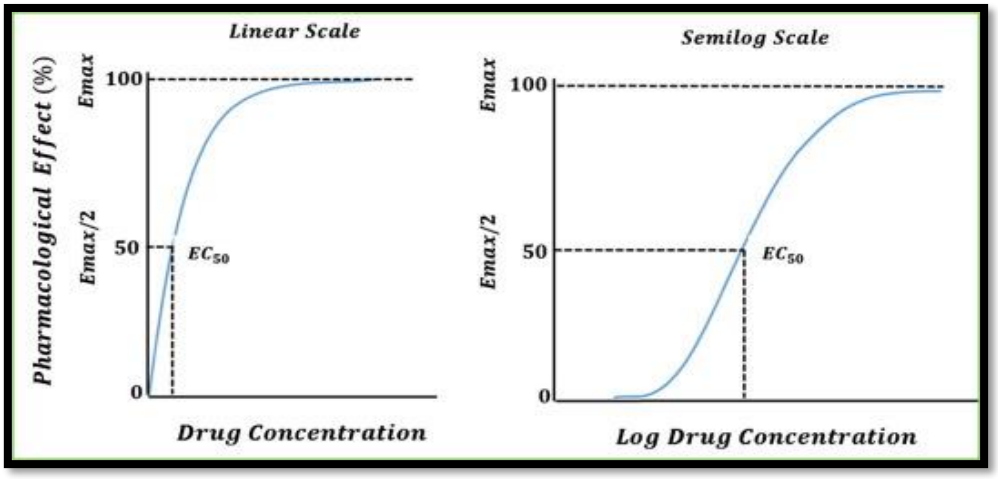


Figure 6: Potency-Drug Concentration Graph

2. **Efficacy:** It is the maximum response a drug that can be achieved when it interacts with a receptor. Efficacy is dependent on the intrinsic activity of the drug and in the number of drug-receptor complexes formed.

3. **Drug concentration on receptor binding:** The law of mass action is applied to the kinetics of the binding of drug and receptor molecules.

DRUG +RECEPTOR⟶DRUG-RECEPTOR COMPLEX ⟶BIOLOGICAL EFFECT

It is presumed that the binding of one drug molecule will not alter the binding of following molecules and when the mass action is applied, mathematically it is expressed as

$$\frac{[DR]}{[Rt]} = \frac{[D]}{Kd + [D]}$$

[D]-the concentration of free drug
[DR]- the concentration of bound drug
[Rt]- the total number of receptors
Kd- the equilibrium dissociation constant for the drug from the receptor

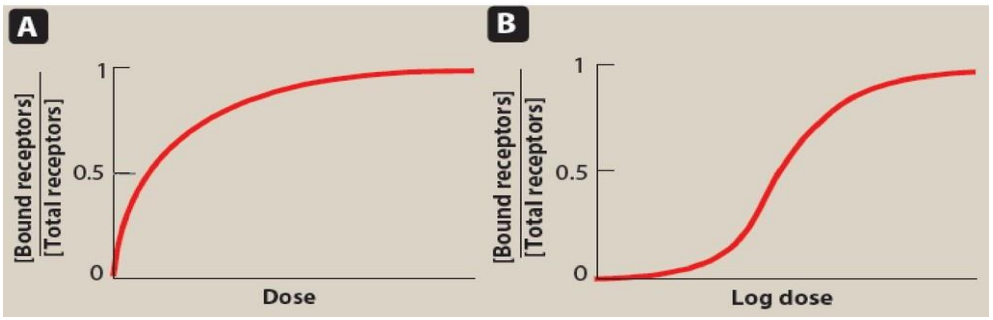


Figure 7: Drug Concentration on Binding Receptor

4. Pharmacologic effect of the binding drug:

The law of mass action is applied,

$$\frac{[E]}{[Emax]} = \frac{[D]}{Kd + [D]}$$

Where,

[E] -the effect of the drug concentration [D]
[Emax] -the maximal effect of the drug

Law of mass action can be applied when the following conditions are met,

1. The magnitude of response is proportional to the number of receptors occupied by the drug
2. Emax occurs when all receptors are bound
3. One molecule of drug binds to only one molecule of receptor

XI. THERAPEUTIC INDEX AND SAFETY TERM

At the beginning of the last century, Ehrlich introduced the concept of the therapeutic index. Since the development of clinical pharmacology and scientific analysis of clinical data, the implications have undergone radical changes. Back then, the therapeutic index (TI) was derived from animal experiments and was defined as the ratio of TD_{5o} to ED_{5o} for some therapeutically compatible effect.

$$TI = \frac{TD_{5o}}{ED_{5o}}$$

The TI is a measure of a drug's safety because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

From the above derivative, TI is a number and an indication of the 'margin of safety'. But in a clinical situation, TI has limitations

Limitations of therapeutic index:

1. Clinical situations with Extrapolation of animal data.
2. A toxic symptom is more relevant than lethality in humans.
3. Drugs may have more than one ED_{5o} which depends on the measure of effectiveness.
4. Some significant toxic symptoms are seen in some individuals only.

Due to these limitations, the term safety margin is more in vogue. Based on this criterion, benzodiazepines, barbiturates and digoxin have a high, moderate and low therapeutic index. Two parameters are needed to calculate the safety margin in humans,

- Effective dose: To calculate the specific effect in most humans, viz. EDmax
- Maximum tolerated dose, which does not produce any ADR, viz. TD_o

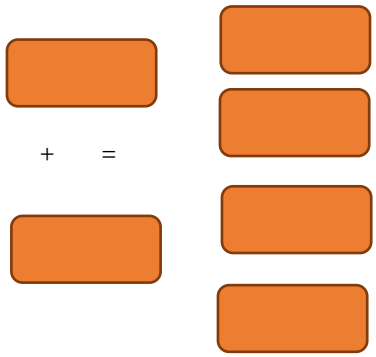
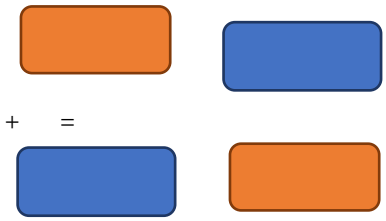
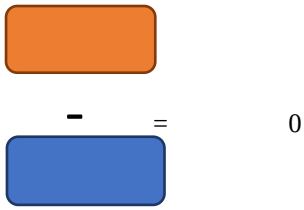
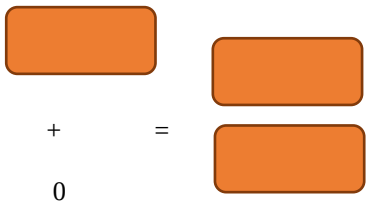
$$TI = \frac{TD_o}{ED\ max}$$

Care is needed while using drugs with low margin of safety.

XII. DRUG-DRUG INTERACTIONS

A drug interaction occurs when one drug is administered with or shortly after another drug and alters the effect of one drug or both drugs. This increases or decreases the effect of the drug or might cause unexpected effects. Consequences of drug-drug interactions are given below,

Table 2: Drug-Drug Interaction

Drug-Drug Interaction	Definition	Example	Representation
Synergism	The interaction of two or more drugs when their combined effect is greater than the sum of the effects seen when each drug is given alone.	Barbiturate drugs when taken with general anaesthetics, alcohol and other sedative-hypnotic drugs can lead to greater adverse effects on the central nervous system	
Additive Effect	The combining effects of two drugs equal the sum of the effects of the two drugs acting independently.	Take aspirin and acetaminophen which is the active ingredient in drugs like Tylenol.	
Therapeutic Antagonism	One drug reduces or blocks the effect of another. This can happen in many ways, for example, drugs can interfere with each other in absorption or uptake by cells in the body	Verapamil is a blocker of L-type Ca channels, but blocks Na channels at high concentrations	
Potentiation	The effect of one drug is increased by the intake of another drug without causing a notable effect. Although, the toxicities of drug B can also be potentiated leading to increased adverse effects.	Diazepam may potentiate the effect of alcohol.	

XIII. FACTORS AFFECTING DRUG RESPONSE

Drug responses can vary due to pharmacokinetic, pharmacodynamic variabilities and genetic differences. Pharmacodynamic variables can be because of genetic factors, tolerance, concurrent diseases affecting the patient, drug interactions and dependence.

1. **Sex**

   - Females have a smaller body size and require doses on the lower side range. They should not be given purgatives or uterine stimulants during menstruation, quinine during pregnancy and sedatives during lactation. Some drugs interfere with the sexual function of males exclusively and should be avoided, if possible, for example, antidepressants, statins and fibrates.

   - **Body weight:** For children based on the body weight the dose of the drug usually varies but for adults the dose of the drug remains the same irrespective of their weight.

2. **Age**

   - **Children:** Response to drugs by neonates differs widely than those of the adults. Some drugs are tolerated by children but cause problems neonates. Examples of drugs associated with problems are chloramphenicol (grey baby syndrome).

   - **Elderly:** Drug use generally requires significant reductions in drug dose reflecting the decline in body function with age. More attention should be given to toxicity and failure of treatment. Patients react differently to medications than young adults, as they age. In the elderly, sometimes distinguishing subtle adverse drug effects from the effects of the disease is often difficult which may lead to prescribing cascade.

3. **Food:** The presence of food, like fatty acids delays gastric emptying and also delays the absorption of certain drugs like rifampicin. Protein malnutrition causes many changes which may affect drug action. Alcohol induces drug-metabolizing enzymes. Calcium in milk interferes with the absorption of tetracyclines.

4. **Biorhythm:** It is the recurring cycle in the physiology or functioning of an organism, such as the daily cycle of sleep and waking. For example, Hypnotics taken at night produce sleep more easily at a lower dose than in the daytime.

5. **Psychological state:** In some patients, inert drugs (Placebo- refers to any therapeutic procedure without any specific activity, given deliberately to affect the patient that can be explained by drugs pharmacological and therapeutic properties) may introduce beneficial effects equivalent to the drug.

6. **Cumulation:** When a drug is excreted slowly from the body and too frequent doses are administered, there may be a build-up of a high concentration of the drug in the body which produces toxicity. For example, digitalis.

7. Tolerance

- A higher dose of a drug is required to produce an effect, which can be ordinarily produced by the normal therapeutic dose of the drug. Natural tolerance may
- Also, be present in some cases.

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