الجمهورية الجزائرية الديمقراطية الشعبية

People's Democratic Republic of Algeria

Ministry of Higher Education and Scientific Research

University of Tiaret

Institute of Veterinary Sciences

PHARMACOLOGY HANDOUT

PHARMACODYNAMIC OF DRUGS

Realised by

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University year

2025 - 2026

Preface

As part of the university activities, I have prepared this handout entitled "The Pharmacodynamics of Drugs."

This document breaks down one of the chapters of general pharmacology. It covers the organic, physical, chemical, and biochemical phenomena that underlie the explanation of the effect obtained after the administration of a drug. Specifically, this chapter explains how a drug produces the desired pharmacological effect by examining: the different mechanisms of action a drug can exert, the types of ligands, drug receptors, transduction, and the dose-response relationship.

This handout aims to be a valuable resource for students, teachers, and practicing veterinarians to better understand the mechanism of action of drugs, which appears to be a crucial parameter in explaining the various possible drug combinations, side effects, and potential drug toxicity.

There were some challenges in writing this handout, particularly regarding the availability of information for different animal species. This latter situation forced us to make a bibliographic synthesis between the data of human pharmacology while supplementing them with the data and particularities of veterinary pharmacology.

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List of abbreviations

DNA :	Deoxyribonucleic acid
cAMP:	Cyclic adenosine monophosphate
AMP:	Adenosine monophosphate
mRNA :	Messenger ribonucleic acid
HCl :	Hydrochloric acid
pH:	Hydrochloric acid
D :	Drug
R:	Receptor
DR:	Drug-Receptor
Kd:	Dissociation constant
Ka:	Association constant
E_{max} :	Maximum of effect
GRKs:	G protein-coupled receptor kinases
PKA:	Protein kinase A
H_2 receptor :	Receptor H2 of histamine
Ri:	Receptor inactive
Ra:	Receptor active
NMDA :	N-methyl-D-aspartate
NO:	Nitric oxide
Ca2+:	Calcium
GPCR :	G-protein coupled receptor

GABA:	Gamma-aminobutyric acid
NE:	Norepinephrine
Ach:	Acetylcholine
GDP:	Guanosine diphosphate
GTP :	Guanosine triphosphate
DAG :	Diacylglycerol
IP3:	Inositol triphosphate
AMPA:	-amino-3-hydroxy-5-méthyl-4-isoxazolepropionic acid
TGF-β :	Transforming Growth Factor-beta
ATP:	Adinosine triphosphate
RNA:	Ribonucleic acid
AP1 :	Activator Protein-1
SP1:	Specificity Protein-1
E :	Effect
C:	Concentration
EC :	Effective concentration
ED:	Effective dose
TD:	Toxic Dose
LD:	Lethal dose

Introduction

Pharmacology is the science that largely deals with the physical and chemical properties, actions, absorption, and fate of chemical substances termed drugs that modify biological function. It is a discipline that touches most topics of human and veterinary medicine and closely interfaces with pharmaceutical science and toxicology (Riviere and Papich, 2018).

Pharmacodynamics indicates the actions of the drug on the body, such as mechanism of action and therapeutic and toxic effects. It is the study of the interaction of the drug molecule with the biological target, often referred to generically as the receptor. This forms the basis of Pharmacology in that all therapeutic application of drugs has a common root in pharmacodynamics (Lista and Sirimaturos, 2021).

Pharmacodynamics is the study of the biochemical and physiological effects of drugs (or any foreign substance), and the mechanisms of action. More generally this principle applies to the relationship between the concentration in the blood and the effect obtained (Wingard et al., 1991).

Clinicians are most concerned with pharmacodynamics, they want to know how drug dosage, route of administration, and frequency of administration can be chosen to minimize the likelihood of unwanted drug effects and maximize the probability of therapeutic success. Because drug effects are related to drug concentrations, understanding and predicting the time course of concentrations can be used to help optimize therapy (Greenblatt et al, 2016).

Chapter 1
General consideration of drug action

The biophase is the site where the drug exerts its action. Most drugs must leave the plasma to reach different tissues to exert their effect. This can cause a delay between time taken to reach a plasma concentration and the onset of clinical effect known as 'effect hysteresis' (Rimmington, 2020)

Drug molecules usually reach the biophase by passive diffusion along a concentration gradient from the plasma, which can be assumed to be part of the initial distribution volume. When the free drug concentration in the plasma decreases below that in the biophase the process is reversed, so that drug re-enters the plasma, thus terminating the effect. Drug molecules in the biophase may (Hull, 1979):

(1) remain freely dissolved in the biophase,

(2) bind to specific receptors, thus exerting the effect,

(3) bind to non-specific, inactive sites such as tissue proteins,

(4) undergo biotransformation without returning to the plasma,

(5) be excreted without returning to the plasma,

(6) return unchanged to the plasma.

In pharmacology, the interaction between drugs and receptors forms the ground for our understanding of how medicines produce their effects within the body. Drug-receptor interactions are at the core of pharmacodynamics, shedding light on how drugs exert their therapeutic actions, while also revealing the complexities of side effects and potential adverse reactions (Shimla, 2023).

1. Pharmacodynamis effects:

The pharmacodynamic effect is a measurable, reproducible, functional or organic change caused by a drug in a biological system called an effector. This term "pharmacodynamic effect" should be reserved for the action of the drug at elemental levels, such as molecules or cells. It is the support of the mechanism of action of the active ingredient. The main pharmacodynamic effect is responsible for the response as

far as it constitutes the mechanism of action that leads to the modifications of the organism that interest us. (Secco et al., 2020).

Effects can be classified as direct or indirect and immediate or delayed.

1.1. Direct effects :

They are usually the result of drugs interacting with a receptor or enzyme central to the effect's pathway. Beta-blockers inhibit receptors that directly modulate cAMP levels in smooth muscle cells in the vasculature (Marino et al., 2023).

1.2. Indirect effects :

Theses effects result from drugs interacting with receptors and proteins of other biologic structures significantly upstream from the end biochemical process that produces the drug effect. Corticosteroids bind to nuclear transcription factors in the cell cytosol, which translocate to the nucleus and inhibit DNA transcription to mRNA encoding for several inflammatory proteins (Ramamoorthy and Cidlowski, 2016).

1.3. Immediate effects :

They are usually secondary to direct drug effects. Neuromuscular blocking agents such as succinylcholine, which consists of 2 acetylcholine molecules linked end to end by their acetyl groups, interact with the nicotinic acetylcholine receptor on skeletal muscle cells and leave the channel in an open state, resulting in membrane depolarization and generation of an action potential, muscle contraction and then paralysis within 60 seconds after administration (Jonsson, 2006).

1.4. Delayed effects :

Delated effects can be secondary to direct drug effects. Chemotherapy agents that interfere with DNA synthesis, like cytosine arabinoside, which is used in acute myeloid leukemia, produce bone marrow suppression that occurs several days after administration (Marino et al., 2023).

A drug produces one or more pharmacodynamic effects on the body, at doses that may vary, a benefit at one dose and harm at another (hormesis) (Currie, 2018). It has:

- Primary effect, used therapeutically
- Side effects, which may be beneficial, insignificant, bothersome, or harmful.

In medicine, a side effect is an effect, whether therapeutic or adverse, that is secondary to the one intended. Although the term is predominantly employed to describe adverse effects, it can also apply to beneficial, but unintended consequences of the use of a drug (Secco et al., 2020).

The same pharmacodynamic effect can be produced by several drugs; all of these drugs together constitute a pharmacological class. However, drugs of the same pharmacological class share the main effect (figure 1), while side effects may differ depending on the substance (Dangoumau et al., 2006).

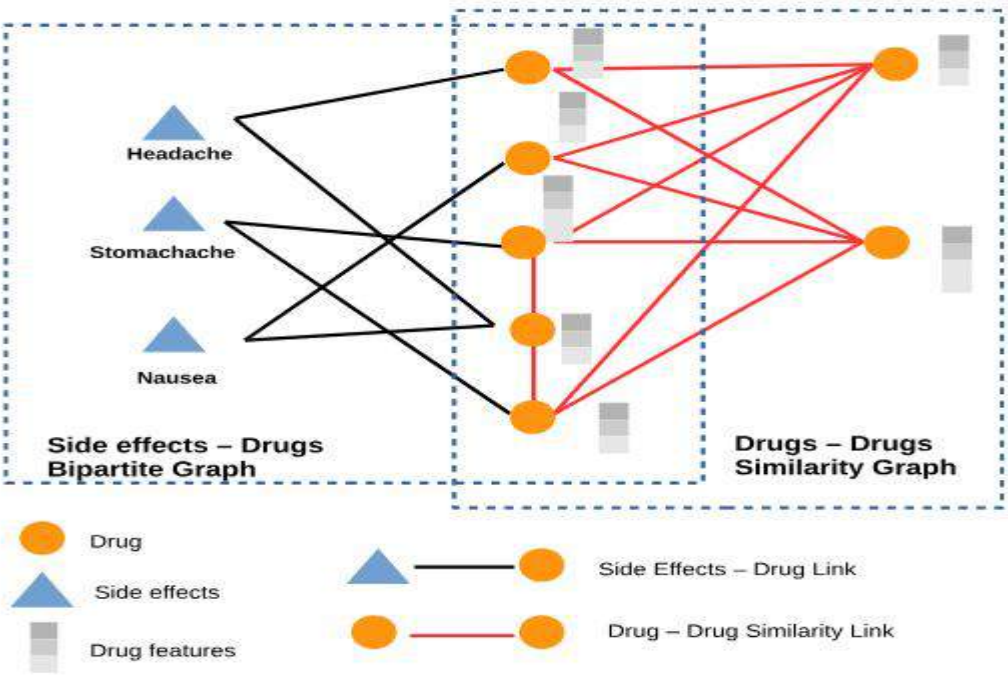

Figure 1: An example of side effect-drug bipartite graph and drug-drug similarity graph (Timilsina et al., 2019).

The goal is to have the effect of the drug be therapeutic. Generally speaking, drugs have two kinds of effects: therapeutic effects and side effects. The ideal drug for any therapeutic indication would have only therapeutic effects and no side effects. We all know that in the real world, there are no such perfect drugs, but the best and most commonly used medications have a very high "therapeutic to side effect ratio" (Thomas and Karmer, 2003).

Some adverse effects are so common and so readily associated with drug therapy that they are identified very early during clinical use of a drug. By contrast, serious adverse effects may be sufficiently uncommon that they escape detection for many years after a drug begins to be widely used. So practitioners must be continuously vigilant to the possibility that unusual symptoms may be related to specific drugs, or combinations of drugs, that their patients receive (Roden, 2025).

2. Mechanism of actions of drugs:

Drugs commonly alter the rate or magnitude of an intrinsic cellular response rather than create new responses. But even this on its own may have significant toxicological and medical effects (Kamepalli et al., 2025).

Most of drug effects are induced by the interaction of a drug molecule with specific molecular structure in the body known as receptors. However, some drug effects are non-receptor mediated and are caused by the particular physical or chemical properties of the drug molecule (Blumenthal and Garisson, 2011). (Figure 2)

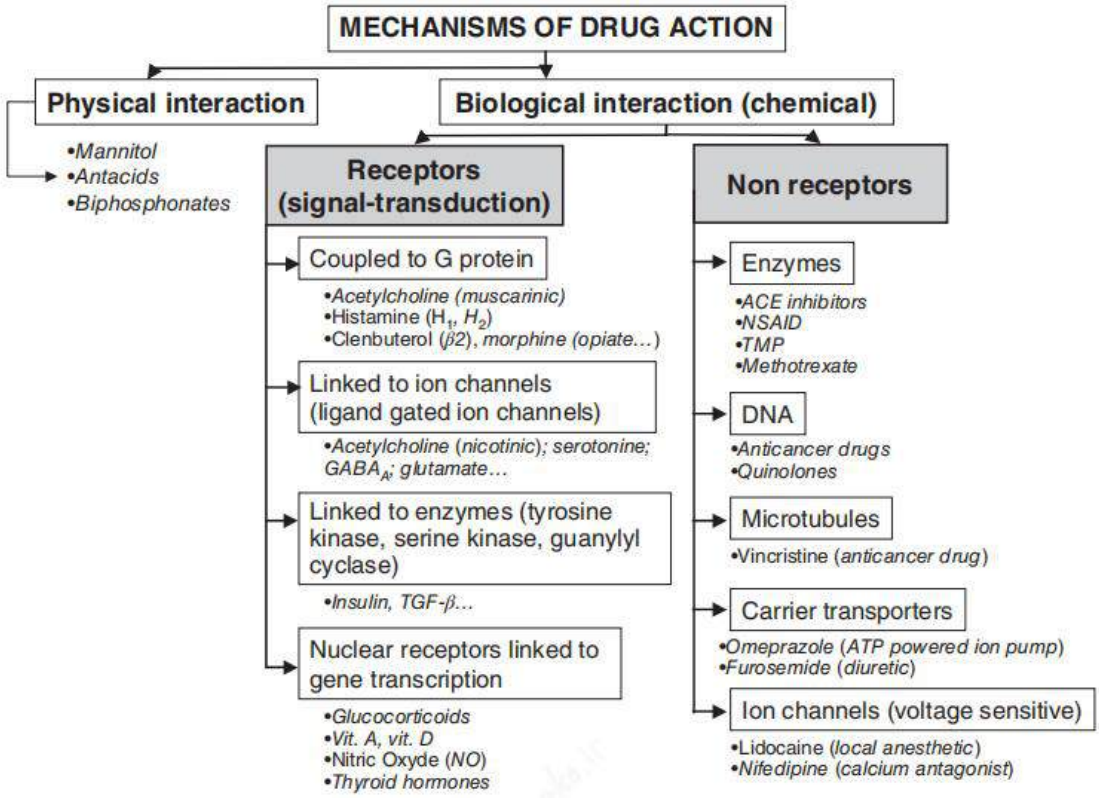

Figure 2: Mechanisms of drug action (Toutain, 2018).

2.1. Non-receptor - mediated effects:

A few agents produce their therapeutic effects without receptor interactions. Most agents that do not rely on receptors for effect seem to intead rely on their physical or chemical properties to alter normal body function. These drugs involve physical phenomena (e.g., the protective, absorbent and lubricating properties of agents applied topically to the skin and mucous membranes, laxatives), chemical phenomena with an endogenous or exogenous substance (e.g., neutralization of HCl in the stomach by antacids (Toutain, 2018)), and physicochemical phenomena (e.g., surfactants or surfactants. Detergents, emulsifiers, antifoaming agents, and several antiseptics and disinfectants have surfactant properties). (figure 3)

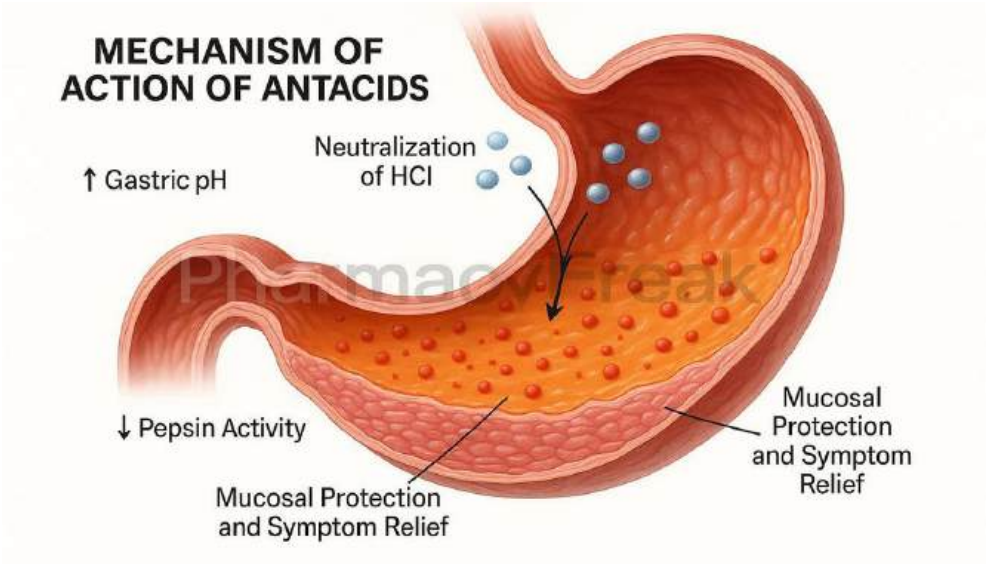

Figure 3: Mechanism of action of antiacid (Rajput, 2025).

Consider the use of dextran 70 as a plasma expander. It is used primarily because of its osmotic properties and relatively slow elimination. Another example, is the use of ammonium chloride to decrease th pH of urine. This is occasionaly useful to enhance the elimination rate of some basic compounds and is based entirely on the acid-base chemistry of the compounds in urinary fluid (Dick, 2011).

2.2. Receptor mediated effects:

The effects of most drugs result from their interaction with macromolecular components of the organism either of the host or of the pathogen. These interactions alter the function of the pertinent component and initiate the biochemical and physiological changes that are characteristic of the response to the drug.The term drug receptor or drug target denotes the cellular macromolecule or macromolecular complex with which the drug interacts to elicit a cellular response, i.e., a change in cell function (Blumenthal and Garisson, 2011 ; Toutain, 2018).

Humans have long used plant and animal extracts for their medicinal properties but until the end of the 19th century their actions were often explained in a speculative

manner. The systematic study of drugs did not begin until the 1860s, and the concept of receptors as the target of their effects in the body only emerged at the end of the 19th century from the brilliant and independent studies of John Newport Langley (1852-1925) and Paul Ehrlich (1854-1915) (Pruell et al., 2009). Proof of the receptor concept lagged behind theory, and it would take the introduction of the B-adrenergic antagonist, propranolol, in 1965 to provide the data necesary to completely convince the scientific community that recepor truly exist. Since then, specific molecular targets of action have been identified for nearly all drugs, and evidence for the recpetor theory continues to grow (Dick, 2011).

The concept and study of drug-target binding kinetics have emerged since the evolution of modern pharmacology (Figure 4). In the 19th century, the law of mass action was firstly described in chemical reactions, while in the year 1900, Paul Ehrlich introduced the term "receptor", symbolizing the era of modern pharmacology. Later in 1913, Ehrlich also coined the phrase "***corpora non agunt nisi fixata***" : a drug will not work unless it is bound (Kaufmann, 2008).

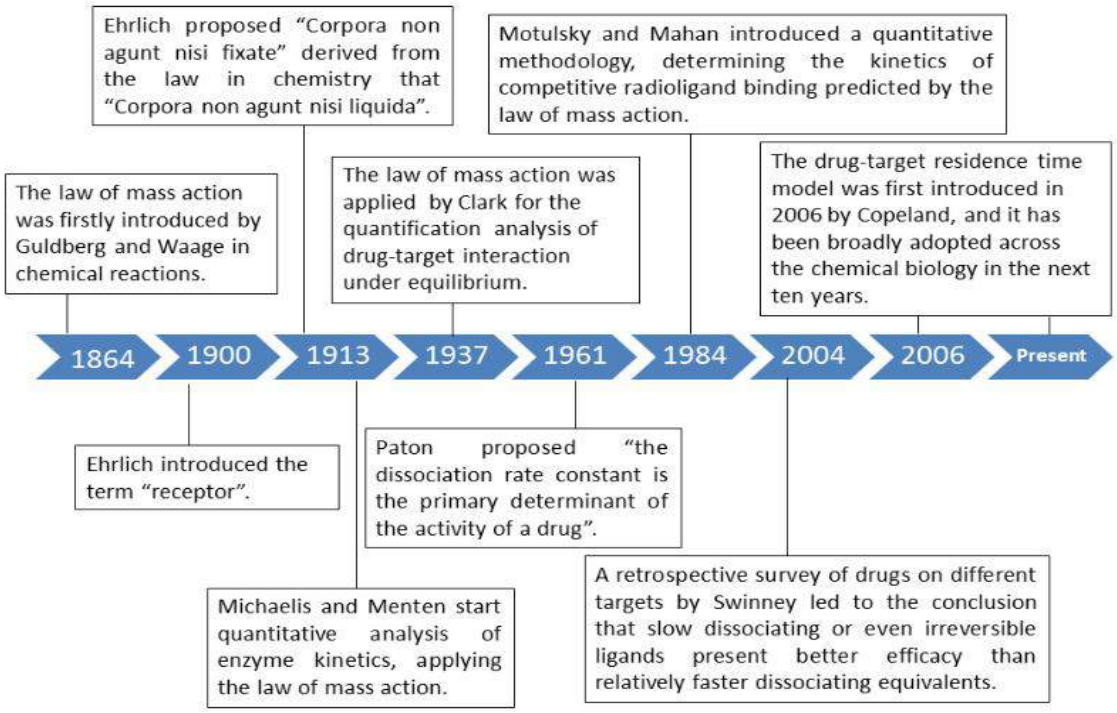

Figure 4: The emergence of binding kinetics studies (Xia, 2018).

In the realm of modern medicine, the effectiveness and safety of pharmaceutical interventions depend largely on the interactions between drugs and their respective cellular targets, primarily protein receptors (Shimla, 2023).

From a numerical standpoint, proteins form the most important class of drug receptors. Examples include (Blumenthal and Garisson, 2011 ; Trevor et al., 2015):

- The receptors for hormones, growth factors, transcription factors, and neurotransmitters;
- The enzymes of crucial metabolic or regulatory pathways (e.g., dihydrofolate reductase, acetylcholinesterase, and cyclic nucleotide phosphodiesterases);
- Proteins involved in transport processes (e.g., Na + ,K+ -ATPase); secreted glycoproteins (e.g., Wnts);
- Structural proteins (e.g., tubulin).

Specific binding of drugs to other cellular constituents such as DNA is also exploited for therapeutic purposes. For example, nucleic acids are particularly important drug receptors for certain cancer chemotherapeutic agents and antiviral drugs (Blumenthal and Garisson, 2011 ; Toutain, 2018).

Chapter 2
Receptor and drug-receptor interaction

Many drug receptors are protein macromolecules found primarily in cell membranes, the cytosol, and the nucleus, capable of specifically recognizing and binding endogenous or exogenous mediators (or ligands) making receptors essential components of cell communication and function. Mediator binding triggers a biological response mediated by an amplifier and an effector (Loichot et Grima, 2006 ; Rimmington, 2020 ; Shimla, 2023).

Receptors possess an effector system (also termed signal-transduction pathways). In this they differ from acceptors which are molecules without signaltransduction pathways (e.g., serum albumin), characterized by a binding process that is not followed by a physiological response (Toutain, 2018).

Effectors are molecules that translate the drug-receptor interaction into a change in cellular activity. The best examples of effectors are enzymes such as adenylyl cyclase. Some receptors are also effectors in that a single molecule may incorporate both the drug-binding site and the effector mechanism (Trevor et al., 2015). The first receptors used as drug targets (e.g., histamine receptors) consist of a single binding site that accepts a low molecular weight natural ligand. There are also receptors that are more complex, composed of binding sites including identical or different protein subunits that reserve a natural ligand, itself a mono- or polymeric protein; these receptors are those for growth factors and cytokines (Dutartre, 2001).

1. Drug - receptor interaction :

The interaction of a drug with its receptor is the fundamental event that initiates the action of the drug (Trevor et al., 2015). The basic concepts of drug - receptors interactions can be described by the «lock and key» model in which a receptor structure (the lock) has a region with a particular shaped pocket at which an appropriatly shaped molecule (the key) can interact (figure 5) (Dick, 2011). This key-lock relationship

determines the drug's ability to bind to the receptor and trigger a response (Shimla, 2023).

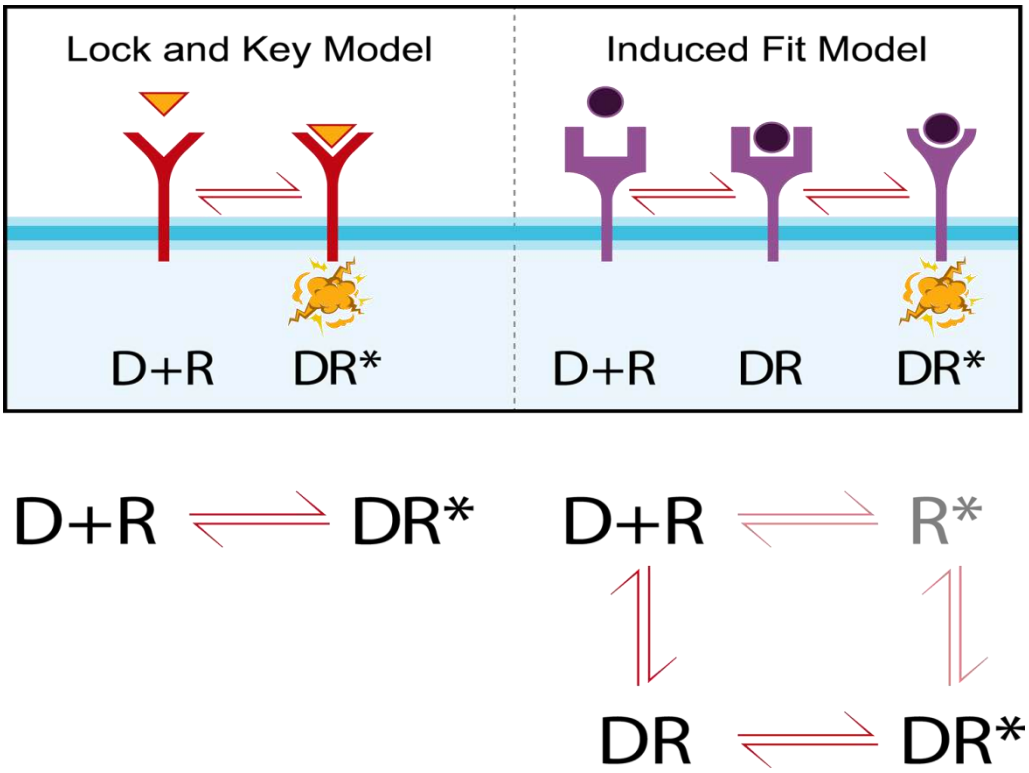

Figure 5: Drug–Receptor Binding Models (Ruby, 2026).

The induced fit model is an alternative way to describe the binding of a drug to its specific receptor. In the induced fit model, unlike the lock and key model, the conformation of the receptor is not completely complementary to the drug during initial binding. Instead, the molecular and chemical interaction between the drug and receptor induces conformational changes in one or both molecules, resulting in a stronger bond (Ruby, 2026).

The receptor site (also known as the recognition site) for a drug is the specific binding region of the receptor macromolecule (Trevor et al., 2015). Receptors exist in at least two states, inactive (R) and active (R*), that are in reversible equilibrium with one another, usually favoring the inactive state. Binding of drug causes the equilibrium to

shift from R to R* to produce a biologic effect (Dangoumau et al., 2006 ; Blumenthal and Garisson, 2011).

$$L + R \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} LR \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} LR*$$

A drug is termed an « ***Agonist*** » if it binds to a site on a receptor protein and activates it to initiate a series of reactions that ultimately result in a specific intracellular response . The concept of interaction at the receptor site is based mainly on the ligand's shape and chemical makeup (Shimla, 2023). Drug-receptor interactions are guided by a variety of molecular forces, including electrostatic interactions, hydrogen bonds, hydrophobic interactions, van der Waals forces, ionic bonds, and covalent bonds, as described in the text below by Toutain (2018) and Ruby (2026):

The electrostatic interaction between a receptor and a drug relies on areas of positive and negative charges or polarity found in both the drug and the receptor. Simple organic elements, such as carbon and hydrogen, found in many drugs tend to be electrically neutral, as electrons are shared equally between dominant carbon and hydrogen atoms, but drugs can also contain molecules of oxygen, nitrogen, phosphorous, and sulfur where electron sharing is unequal. The polar and nonpolar regions of a drug molecule created by its elemental composition impact the interaction with biological receptors, with their own unique regions of polarity. Since binding takes place in an aqueous environment, regions of a receptor may include areas of hydrophobicity or hydrophilicity. The common electrostatic interactions that occur between charged amino acid residues and charged moieties of the drug and a receptor can be categorized as follows:

• ***Hydrogen bonding*** is characterized by the sharing of a hydrogen atom between two electronegative atoms, such as nitrogen or oxygen. Hydrogen bonds between amino acid residues and drug nitrogen and oxygen molecules stabilize drug-receptor

interactions and can also contribute to protein-protein interactions by forming intermolecular hydrogen bonds between interacting proteins.

• ***Hydrophobic interactions*** occur between nonpolar amino acid regions of the receptor proteins and uncharged or aliphatic regions of a drug, such as long strands of hydrocarbons. These residues tend to be located in the interior of the receptor and be composed of hydrophobic amino acid residues.

• ***van der Waals forces*** are weak forces found between transient dipoles that occur from the random motion of electrons in atoms and molecules. These forces contribute to drug interactions with the receptor by stabilizing the close proximity of interacting proteins.

• ***Ionic bonds*** are strong electrostatic interactions that are formed between two molecules of opposite charges in which one atom lacks an electron, called an anion, and the other with a surplus electron, called a cation. The bond is dependent on the degree of ionization of the atoms that form reactive cations and anions. The pH of the local environment and the pK of the drug, which is a summation of the various ionizable groups found in the drug, are critical for the formation of these bonds. In biological organisms, the formation of a duration of an ionic bond is influenced by the presence of inorganic salts in the media that can compete for binding and could limit their formation.

• ***Covalent bonds*** are defined by a mutual but unequal sharing of electrons between atoms. These bonds are typically important for maintaining the structure of organic compounds such as proteins, carbohydrates, and lipids in a biological organism, but they can occur between a drug and a receptor. In the environment of a biological organism, covalent bonds are not easily reversed and are considered irreversible. Thus a covalent drug-receptor binding has a high chance of a prolonged duration of binding and the extension of biological or pharmacological effects.

The interaction of the ligand and its binding site on the receptor complex is governed by two important concepts: ***affinity*** and ***intrinsic activity*** (dick, 2011).

1.1. Affinity:

The binding between the agonist and the receptor is due to weak forces. Drug binding to receptors uses similar chemical bonds as that used for enzyme – substrate interaction: hydrogen bonds coordinate covalent bonding and Vander Waals forces. Examples of covalent bonding involved in drug–receptor interactions are few in number (Hsu and Martin, 2008).

If a molecule is able to interact with the receptor site, it is said to have affinity to taht site (Dick, 2011). The strength of the reversible interaction between a drug and its receptor, as measured by the dissociation constant, is defined as the affinity of one for the other (Dangoumau et al., 2006 ; Blumenthal and Garisson, 2011).

In the laboratory, affinity can be measured as the concentration of a drug that occupies 50% of the available receptors, as suggested by the definition of K_d. K_d measures how tightly a drug binds to its receptor. K_d is the ratio of rate constants for association (k_{on}) and dissociation (k_{off}) of the drug to and from the receptors. At equilibrium, the rate of receptor-drug complex formation is equal to the rate of dissociation into its components receptor + drug (figure 6). The measurement of the reaction rate constants can be used to define an equilibrium or affinity constant ($1/K_d$) (Cross and Plunkett, 2014 ; Higham and Colquhoun, 2024 ; Spassov, 2024). Each drug-receptor combination will have a characteristic K_d value. Drugs with high affinity for a given receptor display a small value for K_d, and vice versa (Bardal et al., 2011).

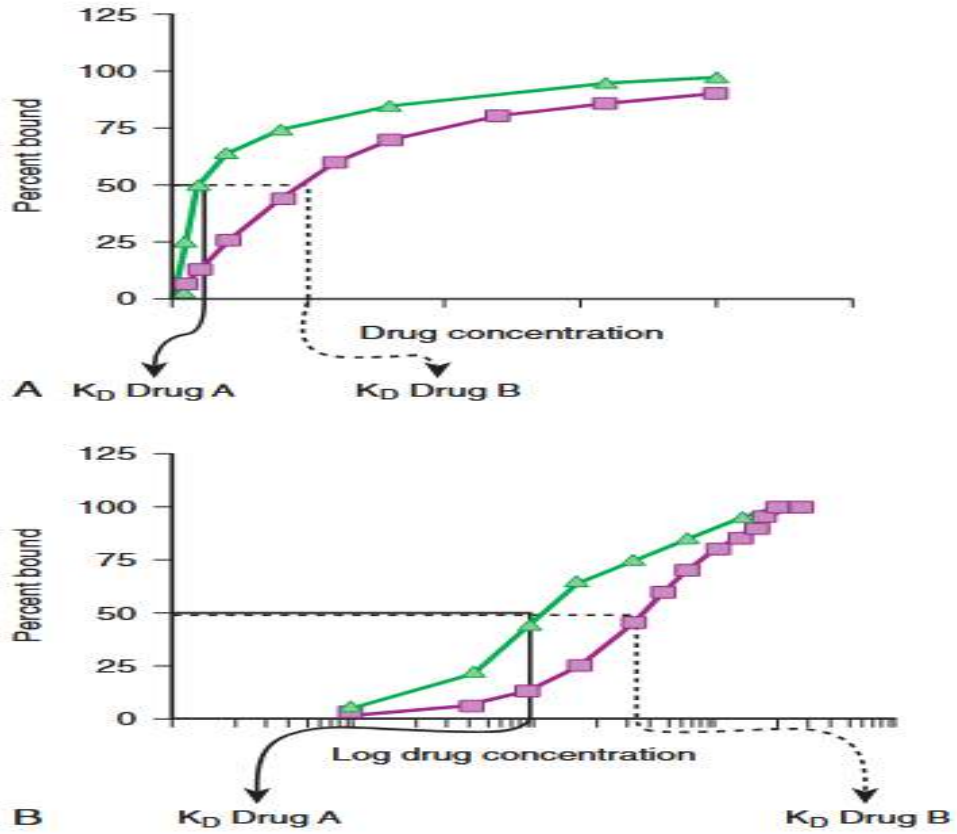

Figure 6: Drug-receptor occupation and Kd (Bardal et al., 2011).

The lifetime of the drug-receptor complex is affected by dynamic processes (conformation changes) that control the rate of drug association and dissociation from the target. A longer residence time explains a prolonged pharmacologic effect. This situation can be a potential disadvantage when it prolongs a drug's toxicity, but has the potential advantage of improved efficacy and flexibility of dosing. For some receptors, transient drug occupancy produces the desired pharmacologic effect, whereas prolonged occupancy causes toxicity (Farinde and Vivian, 2025).

1.2. Intrinsic activity:

In 1956, R.P. Stephenson proposed a modification of receptor theory which has had a lasting influence. He said that in addition to the affinity of a drug for a receptor, an extra parameter was needed to describe the action of an agonist. This extra parameter he called efficacy, which he defined as a measure of the agonist to produce a response once it became bound (Higham and Colquhoun, 2024). However, the intrinsic activity

of a drug further determines its ability to fully or partially activate the receptors. Drugs may be categorized according to their intrinsic activity and resulting E_{max} values (Dangoumau et al., 2006).

The first proposed basis for drug–receptor interaction was the occupancy theory, which suggests that a response occurs only when the receptor is occupied by an agonist and the magnitude of the response (percentage of maximum) is directly proportional to the number of receptors occupied (Lees et al., 2004).

According to the law of mass action, the more receptors the drug occupies, the greater the pharmacodynamic response. However, all receptors need not be occupied to get a maximal response. This principle is the concept of spare receptors. Maximal effects are obtained by less than maximal receptor occupancy by signal amplification (Loichot et Grima, 2004 ; Blumenthal and Garisson, 2011). This might result from 1 of 2 mechanisms. First, the duration of the effector activation may be much greater than the duration of the drug-receptor interaction. Second, the actual number of receptors may exceed the number of effector molecules available. The presence of spare receptors increases sensitivity to the agonist because the likelihood of a drug-receptor interaction increases in proportion to the number of receptors available (Trevor et al., 2015).

The ability of a drug to activate a receptor and generate a cellular response is a reflection of its efficacy. Historically, efficacy has been treated as a proportionality constant that quantifies the extent of functional change imparted to a receptor-mediated response system on binding a drug (Blumenthal and Garisson, 2011).

1.3. Relation structure-activity:

The study of activity-structure relationships constitutes one of the necessary bases for the work of a number of researchers, particularly in medicinal chemistry and researchers for pharmacologists in charge of pre-selecting or selecting a new molecule to make it into a drug (Bryskier, 2006).

Both the affinity of a drug for its receptor and its intrinsic activity are determined by its chemical structure. This relationship frequently is quite stringent. Relatively minor modifications in the drug molecule may result in major changes in its pharmacological properties based on altered affinity for one or more receptors. Exploitation of structure-activity relationships on many occasions has led to the synthesis of valuable therapeutic agents. Because changes in molecular configuration need not alter all actions and effects of a drug equally, it is sometimes possible to develop a congener with a more favorable ratio of therapeutic to adverse effects, enhanced selectivity among different cells or tissues, or more acceptable secondary characteristics than those of the parent drug (Blumenthal and Garisson, 2011).

1.4. Selectivity and specificity of drug:

The words selectivity and specificity can be confusing terms as they are often used synonymously in the medical literature. However, they should not be used interchangeably as each represents a different phenomenon (Mencher and Wang, 2005). For the sake of consistency and clarity, this paper will use the terms as defined below:

- ***Selectivity*** will be used to describe the ability of a drug to affect a particular population, i.e., gene, protein, signaling pathway, or cell, in preference to others. For example a selective drug would have the ability to discriminate between, and so affect only one cell population, and thereby produce an event. The α and β are considered receptor classes of β adrenergic receptors which differ from each other both in ligand selectivity. Yet α1 and α2 in one hand and β1, β2, and β3 in the other hand are considered subtypes. These adrenergic receptor subtypes exhibit differences in both tissue distribution and regulation by phosphorylation by G–protein receptor kinases (GRKs) and PKA. So, pharmacological differences among receptor subtypes are exploited therapeutically through the development and use of receptor-selective drugs. For example, β2 adrenergic agonists such as terbutaline are used for bronchodilation in the treatment of asthma in the hope of minimizing cardiac side effects caused by stimulation of the β1 adrenergic receptor

(Blumenthal and Garisson, 2011). The binding selectivity of a ligand for a receptor R_1 with respect to a receptor R_2 is the ratio of its affinity for R_2 to its affinity for R_1. In practice, L is considered selective for R_1 with respect to R_2 if $K_{d2}/K_{d1} > 100$ (Loichot et Grima, 2006).

- ***Specificity***, a term most often confused with selectivity, will be used to describe the capacity of a drug to cause a particular action in a population. A drug of absolute specificity of action might decrease or increase, a specific function of a given gene or protein or cell type, but it must do either, not both (Mencher and Wang, 2005). An example of such a drug is ranitidine, an H_2 receptor antagonist used to treat ulcers. If, however, a receptor is expressed ubiquitously on a variety of cells throughout the body, drugs acting on such a widely expressed receptor will exhibit widespread effects, and could produce serious side effects or toxicities if the receptor serves important functions in multiple tissues (Blumenthal and Garisson, 2011).

2. Receptor ligands:

The interaction of compounds with the receptor zone has been based on the way in which they interact with the receptor complex and the results of their interactions. these interactions can be roughly classified as receptor ***agonists*** that have both affinity and intrinsic activity, and receptor ***antagonists*** with affinity but lacking intrinsic activity (Dick, 2011 ; Ruby, 2026).

The receptor is postulated to exist partially in the inactive, nonfunctional form (R_i) and partially in the activated form (R_a). Thermodynamic considerations indicate that even in the absence of any agonist, some of the receptor pool must exist in the Ra form some of the time and may produce the same physiologic effect as agonist-induced activity. This effect, occurring in the absence of agonist, is termed constitutive or basal activity. Agonists have a much higher affinity for the R_a configuration and stabilize it,

so that a large percentage of the total pool resides in the R_a–D fraction and a large effect is produced (Katzung, 2021).

2.1. Type of agonists:

There are three primary types of agonists: full, partial, and inverse (Ruby, 2026). (figure 7)

2.1.1. Full agonist:

To be a good agonist at a specific receptor site requires good affinity ans a good activity. Many agonist drugs, when administered at concentrations sufficient to saturate the receptor pool, can activate their receptor-effector systems to the maximum extent of which the system is capable; that is, they cause a shift of almost all of the receptor pool to the R_a–D pool (Dick, 2011 ; Katzung, 2021).

2.1.2. Partial agonist:

Drugs with good receptor affinity but intrinsic activity that is less than the normal endogenous agonist are termed partial agonists because their response at the receptor is less than the endogenous agonist or less than a particular response from an exogenously administred standard agonist (Dick, 2011). Because they occupy the same receptor site, partial agonists can also prevent access by full agonists (Katzung, 2021).

2.1.3. Inverse agonist:

Many receptors exhibit some constitutive activity in the absence of a regulatory ligand; drugs that have stronger affinity for the R_i than for the R_a state and stabilizes a large fraction in the R_i–D (inactive conformation) are termed inverse agonists. Note that partial agonists and inverse agonists that interact syntopically with a full agonist will behave as competitive antagonists (Blumenthal and Garisson, 2011).

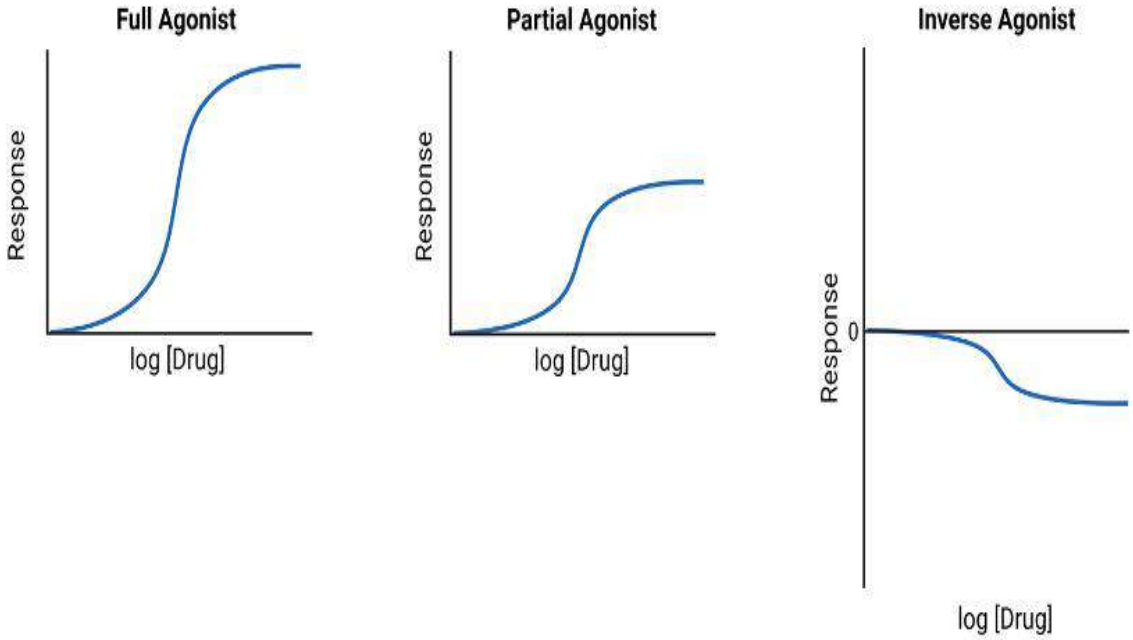

Figure 7 : Types of agonists (Ruby, 2026).

2.2. Types of antagonists:

Some drugs produce their effects by interaction at the receptor complex, but instead the stimulation of the receptor or mimicking the normal endogenous ligand for that receptor, they bolck or decrease agonist interaction at the receptor zone (Loichot et Grima, 2006 ; Dick, 2011). The ways in which drugs act as antagonists can be classified into several general mechanisms, including the following:

2.2.1. Pharmacologic antagonist:

The majority of antagonists used as drug therapy are pharmacologic antagonists that act by directly interfering with anagonist's ability to activate its molecular target. The antagonist prevents agonist binding or agonist activation of the receptor and inhibits the biologic effects generated by the agonist (Bardal et al., 2011). The interaction between antagonist and agonist can take several forms:

a. Competitive antagonist = competitive surmountable antagonism:

The antagonist competes directly for the target receptor with the agonist molecule. These interactions will follow the law of mass action and the same general principles described earlier, with the added facet that now two drugs are competing for receptor occupancy. As the concentration of antagonist increases, the number of antagonist-receptor complexes increases and the number of agonist-receptor complexes decreases. Therefore the agonist effect decreases (Bardal et al., 2011). For example, acetylcholine receptor blockers such as atropine are antagonists because they prevent access of acetylcholine and similar agonist drugs to the acetylcholine receptor site and they stabilize the receptor in its inactive state (Kaatzung, 2021).

A competitive antagonist binds reversibly to a receptor's active site. This binding can be overcome by increasing the concentration of agonist, to outcompete the antagonist. The concentration of agonist needed to outcompete an antagonist will, in part, relate to antagonist affinity (McDonald and Lambert, 2021). The characteristic pattern of such antagonism is a parallel shift to the right of the agonist dose-response curve (figure 8) with no change in the maximal response (Blumenthal and Garisson, 2011). The concentration of antagonist that reduces the agonist response to 50% of maximum is the **IC_{50}**, one index for quantifying antagonist effectiveness (Bardal et al,. 2011).

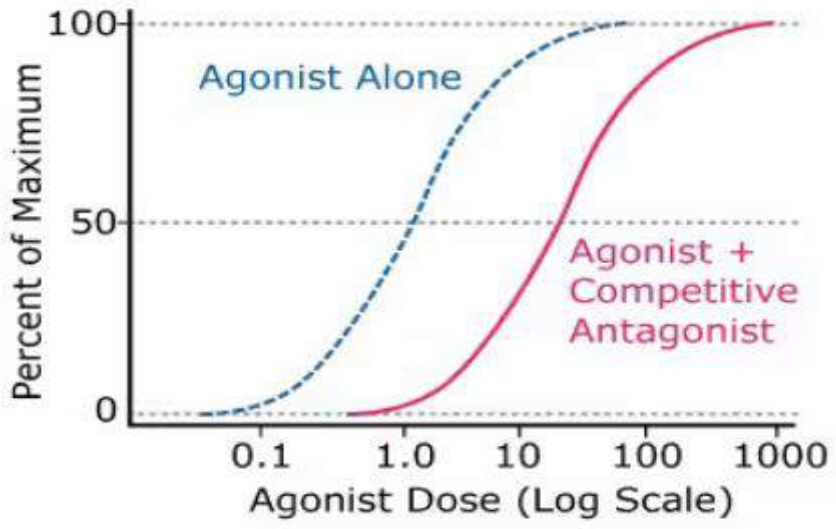

Figure 8: Effect of a competitive (reversible) antagonist (www.sigmaaldrich.com).

b. Non competitive antagonist:

A noncompetitive antagonist binds irreversibly to a receptor. Noncompetitive antagonists do not directly compete with the agonist for binding at the same binding site but nevertheless impair the ability of an agonist to bind to or activate the receptor, and thus they prevent a response (Katzung, 2021). Because agonists and antagonists bind at distinct sites, increased concentrations of an agonist fail to achieve the E_{max} (figure 9) in the presence of a fixed concentration of a noncompetitive antagonist; however, the EC_{50} of the agonist remains the same (Ruby, 2026).

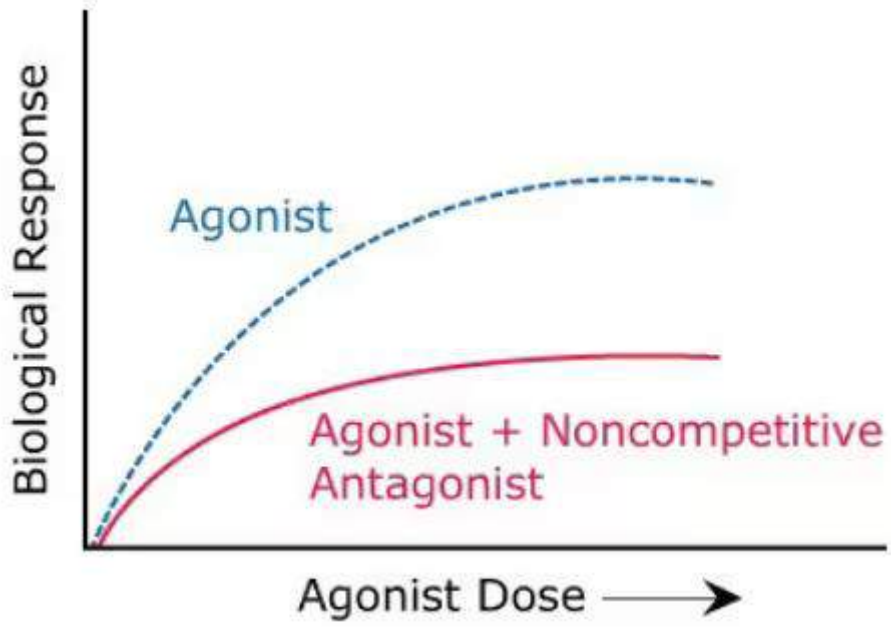

Figure 9: Effect of a noncompetitive (irreversible) antagonist (www.sigmaaldrich.com).

Ketamine is a non-competitive antagonist of NMDA receptors, an ionotropic glutamate receptor. Its antagonism is based on the blockage of the channel, whereas the agonist binding site for the NMDA receptor is located on the extracellular surface (McDonald and Lambert, 2021).

Noncompetitive antagonism can also be produced by another type of drug, referred to as an *allosteric* or *allotopic antagonist*. This type of drug produces its effect

by binding to a site on the receptor distinct from that of the primary agonist causing a conformational change in the receptor complex that may alter the conformation of the binding site of the normal agonist, thereby changing the affinity of the receptor for the agonist (Dick, 2011). In the case of an allosteric antagonist, the affinity of the receptor for the agonist is decreased by the antagonist. In contrast, a drug binding at an allosteric site could potentiate the effects of primary agonists; such a drug would be referred to as an allosteric agonist or co-agonist (May et al., 2007).

2.3. Physiologic (Functional) Antagonists:

Physiologic antagonists represent another type of antagonism in which the antagonist does not interact directly with the actions of the agonist at its molecular target. The agonist and antagonist each act on different molecular targets, but physiological antagonist activates a receptor that is physiologically opposed to the desired physiological response mediated by an agonist–receptor interaction (Hsu and MArtin, 2008 ; Ruby, 2026).

Epinephrine and histamine are good examples of physiologic antagonists. Histamine is a vasodilator and bronchoconstrictor. Histamine release in anaphylactic reactions can cause hypotension and respiratory compromise. Epinephrine supports blood pressure and causes bronchodilation but does not act through the histamine receptor. Thus, epinephrine is given as acute treatment for anaphylactic reactions in part because it is a physiologic antagonist to histamine (Bardal et al., 2011).

2.4. Chemical antagonism:

Chemical antagonists do not act at the receptor level, but rather there is a chemical or physical interaction between the drug and the endogenous target substance. This type of antagonism often does not require animal tissue to be demonstrated, and has been used to treat heavy metal intoxication (Hsu and MArtin, 2008 ; Bardal et al., 2011).

The figure below (figure 10) resume the different types of antagonists.

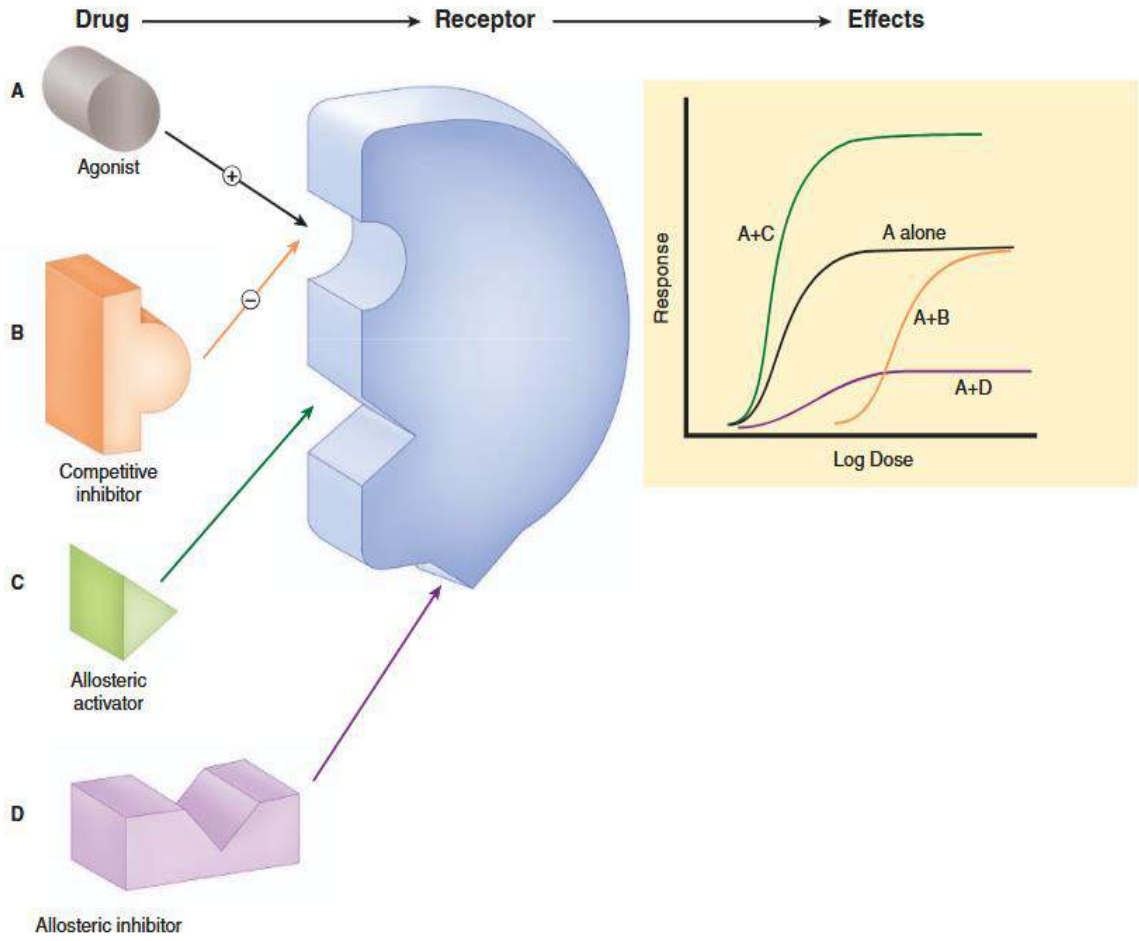

Figure 10: Drugs may interact with receptors in several ways (Blumenthal and Garisson, 2011).

An agonist-antagonist is a drug that exhibits some properties of an agonist and some properties of an antagonist, thereby reversing the effect of the agonist. Antagonistic effects are usually dose dependent. The analgesic nalbuphine is one example of such compounds, which acts as an agonist at opioids κ-receptors and as antagonist at opioids μ-receptors (Dick, 2011 ; Muir, 2015).

3. Signal transduction:

Physiological receptors have at least two major functions, ***ligand binding*** and ***message propagation*** (i.e., signaling). These functions imply the existence of at least two functional domains within the receptor: a ligand-binding domain and an effector domain (Blumenthal and Garisson, 2011).

In many cases this is because the drug is not able to interact directly with the cellular mechanisms eliciting the response (figure 11). Instead, the drug must rely on intermediaries to relay (transduce) the drug signal to the cellular communication (second messenger signaling) and effector systems that ultimately cause the response (Bardal et al., 2011).

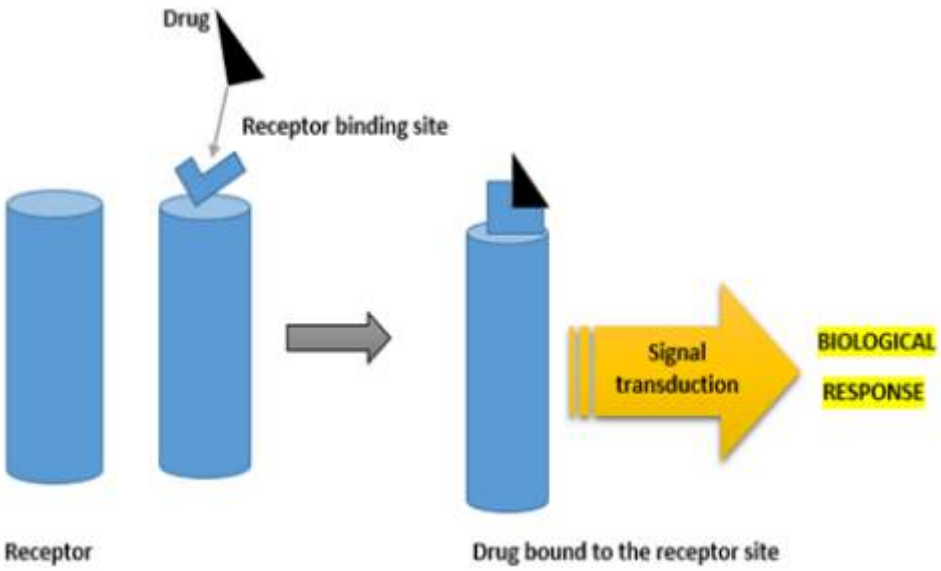

Figure 11: Signal tranduction (Thirumalai et al., 2021).

Many drugs target the extracelluar ligand-binding domain of physiological receptors. The regulatory actions of a receptor may be exerted directly on its cellular target(s), on effector protein(s), or may be conveyed by intermediary cellular signaling molecules called transducers. The receptor, its cellular target, and any intermediary

molecules are referred to as a ***receptor-effector system*** or ***signal transduction pathway*** (Blumenthal and Garisson, 2011).

Conformational changes throughout the structure of the receptor following drug binding facilitate the transduction of molecular signals to modify or modulate the function of the cell. Note that the final change in function is accomplished by an effector mechanism. The effector may be part of the receptor molecule or may be a separate molecule. A very large number of receptors communicate with their effectors through coupling molecules (Katzung, 2021 ; Shimla, 2023).

Frequently, the proximal cellular effector protein is not the ultimate physiological target. The dynamic process often involves multiple transducer cellular proteins recruited to the effector domain of the receptor to coordinate an amplified intracellular signal. Rather an enzyme, ion channel, or transport protein that creates, moves, or degrades a small molecule (e.g., a cyclic nucleotide, inositol trisphosphate, or NO) or ion (e.g., Ca2+) termed a second messenger. If the effector is an ion channel or ion pump, the effect of ligand binding can be a change in membrane potential that alters the excitability of the cell. Second messengers can diffuse in the proximity of their synthesis or release and convey information to a variety of targets, which may integrate multiple signals (Blumenthal and Garisson, 2011 ; Ruby, 2026).

Receptors and their associated effector and transducer proteins also act as integrators of information as they coordinate signals from multiple ligands with each other and with the differentiated activity of the target cell. Thus, the distinct patterns of integration of signal transduction systems within target cells can lead to a variety of pharmacodynamic effects that result from functional interactions downstream from the receptors. For example, signal transduction systems regulated by changes in cyclic AMP (cAMP) and intracellular Ca2+ are integrated in many excitable tissues leading to different effects on cardiac myocyts and smooth muscle cells (Blumenthal and Garisson, 2011).

4. Types of receptors:

Receptors for physiological regulatory molecules can be assigned to four functional families whose members of the same family share similar molecular structures and the nature of the transduction mechanism (Blumenthal and Garisson, 2011 ; Thirumalai et al., 2021). So, some identified receptor subtypes differ only in a few amino acid in their overall protein structure, which may prove insequential (Dick, 2011).

4.1. G Protein-Coupled Receptors (GPCRs):

These are the most numerous (more than 80%) and generally the best known. Also known as ***seven transmembrane receptors*** (7TM receptors) (figure 12) because they span the plasma membrane as a bundle of seven α-helices. GPCRs are responsible for detecting specific extracellular ligands and initiating an intracellular response (Hsu and Martin, 2008 ; Dick, 2011).

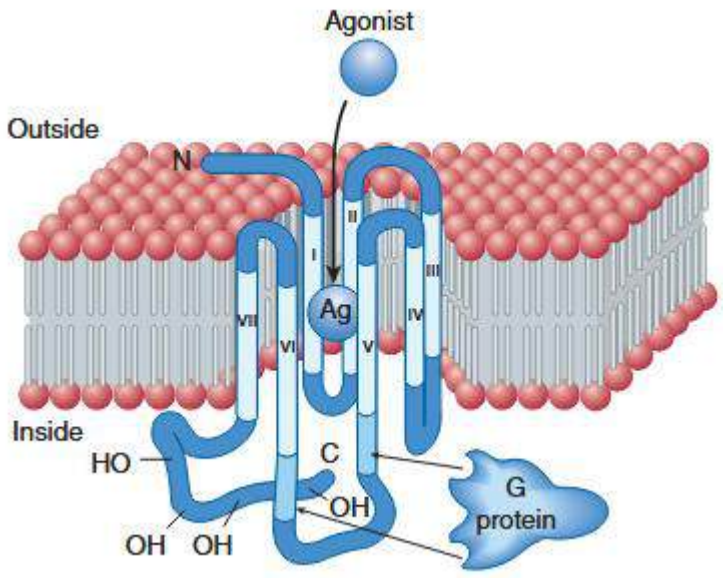

Figure 12 : Transmembrane topology of a typical "serpentine" GPCR (Katzung, 2021).

The GPCR family is made up of about 800 receptors in humans (table 1) and they are classified into five major groups, namely classes A (the largest group), B, C, frizzled, and adhesion (Thirumalai et al., 2021). Included among the ligands for GPCRs

are neurotransmitters such as ACh, biogenic amines such as NE, all eicosanoids and other lipid signaling molecules, peptide hormones, opioids, amino acids such as GABA, and many other peptide and protein ligands. Because of their number and physiological importance, GPCRs are the targets for many drugs; perhaps half of all non-antibiotic prescription drugs act at these receptors. (Blumenthal and Garisson, 2011).

Table 1 : G protein-coupled receptor families (Nürnberg et al., 2024).

Family	Examples for family members	Examples for ligand	G protein coupling	Total number of receptors
Classe A	$Alpha_{2A}$	norepinephrin	$G_{\alpha i}$	719
	MOR	enkephaline	$G_{\alpha i}$	
	Rhodopsin	11-cis retinol	$G_{\alpha t(r)}$	
Classe B	GL-R	glucagon	$G_{\alpha s}$	15
	CALCR	calcitonin	$G_{\alpha s}$, $G_{\alpha q}$, $G_{\alpha 11}$	
	GPR64	orphan	$G_{\alpha s}$, $G_{\alpha q}$, ?	
Classe C	$GABA_{B1}$	γ-Aminobutyric acid	$G_{\alpha i}$	22
	TAS_1R_1	Monosodium glutamate	$G_{\alpha gust}$	
	GPR 1 58	orphan	?	
Adhesion	GPR56	Collagen III	$G_{\alpha 12}$, $G_{\alpha 13}$	33
	GPR113	orphan	?	
	GPR128	orphan	?	
Frizled	SMO	Sonic hedgehog	$G_{\alpha s}$, $G_{\alpha q}$, $G_{\alpha i}$	11
	FZD2	wingless		
	FZD3	wingless		

The heterotrimeric G protein is composed of an alpha, beta, and gamma protein subunit. The beta and gamma subunits serve to localize the complex and mediate interactions with the G protein-coupled receptor. The alpha subunit is the site of GDP-GTP molecule interactions (Ruby, 2026). When a lignad binds to the extracellular binding site, a conformational chnage occurs that triggers the substitution of GTP on the G-protein in place of GDP. This then activates the G-protein complex, allowing the separation of the G-protein from the transmembrane protein. The G-protein can then migrate and interact with various effector macromolecules, leading to their activation or inhibition (figure 13). After that, this protein undergoes (i) hydrolysis, converting the GTP to GDP and deactivating the effector molecule and (ii) recombines with the transmembrane protein in preparation for another round of activation (Dick, 2011).

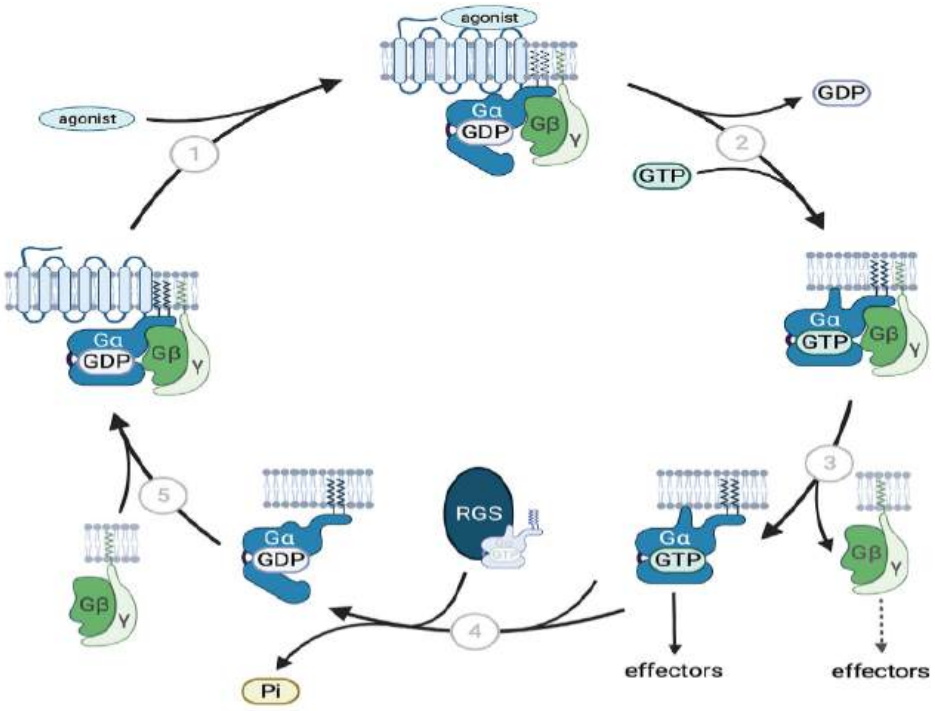

Figure 13 : The principle of the activation/ inactivation cycle of G proteins by GPCR (Nürnberg et al., 2024).

G-proteins may act directly on an ionic channel or activate an enzymatic system to release a range of second messengers, which ultimately permits certain ions to enter

or leave the cell (Toutain, 2018). Three pathways tend to predominate including (Figure 14):

- Gs (stimulatory) receptors that activate adenylyl cyclase to increase cAMP and the activation of protein kinase A (PKA);
- Gi (inhibitory) receptors that inhibit adenylyl cyclase to reduce both cAMP levels and PKA activity;
- Gq receptors that activate phospholipases to cleave PIP2 (phosphatidylinositol 4,5-bisphosphate) into DAG (diacylglycerol) and IP3, which in turn stimulates calcium release from the endoplasmic reticulum. In parallel, DAG and calcium activate protein kinase C enzymes (Ruby, 2026).

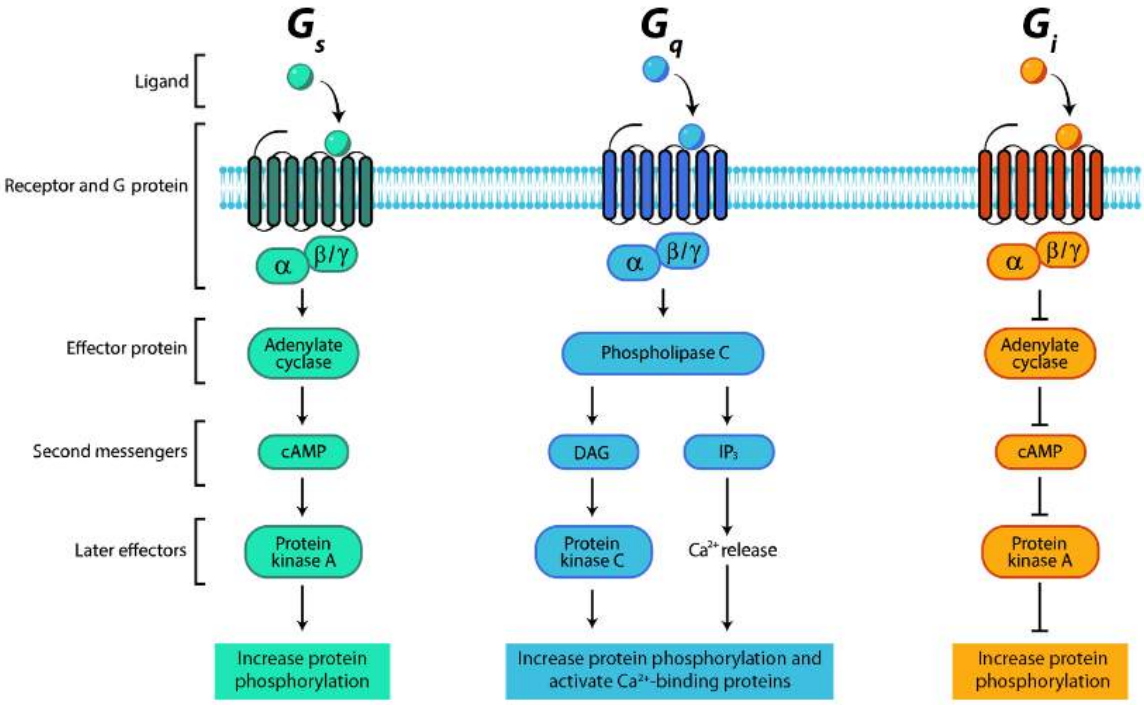

Figure 14: G Protein-Coupled Receptor Subclasses (Ruby, 2026).

Approximately 30% of drugs on the market act on G protein-coupled receptors (GPCRs), making this gene family the most targeted. Furthermore, this family constitutes a large reservoir of potential target, a significant proportion of which do not yet have an identified endogenous ligand (Sebag et Pantel, 2012).

4.2. Ligand-gated ion channels:

Ligand-gated ion channels are membrane proteins that are fundamental signaling molecules in neurons. These molecules are localized in the plasmalemma and on intracellular organelles and are gated by both intracellular and extracellular ligands (Westbrook, 2012).

Both multimeric and symmetrical, these transmembrane receptors form a central aqueous pore that is selectively permeable to specific ions such as Ca2+, K+, and Na+ (Ruby, 2026). They allow the passage of ions from one side of a membrane to another. Channels can exist in the open, closed, or inactive state, which represent different conformations of the channel protein. Drugs may affect the function of these channels by (Alexander et al., 2011 ; Blumenthal and Garisson, 2011) :

(i) directly opening or closing the channel (***ligand gated channels***). Example: Acetylcholine or glutamate (or agonists such as AMPA and NMDA) and inhibitory neurotransmitters such as glycine or γ-aminobutyric acid.

(ii) influencing the voltage-dependent characteristics of the channels (***voltage gated channels***) and the amount of time the channel spends in a given state. Example: Lidocaine.

(iii) generating second messengers (***second messenger gated***) that subsequently open or close the channel. Example: Drugs that block the hyperpolarization cyclic nucleotide gated channel in the sinoatrial node and thereby reduce heart rate. (figure 15)

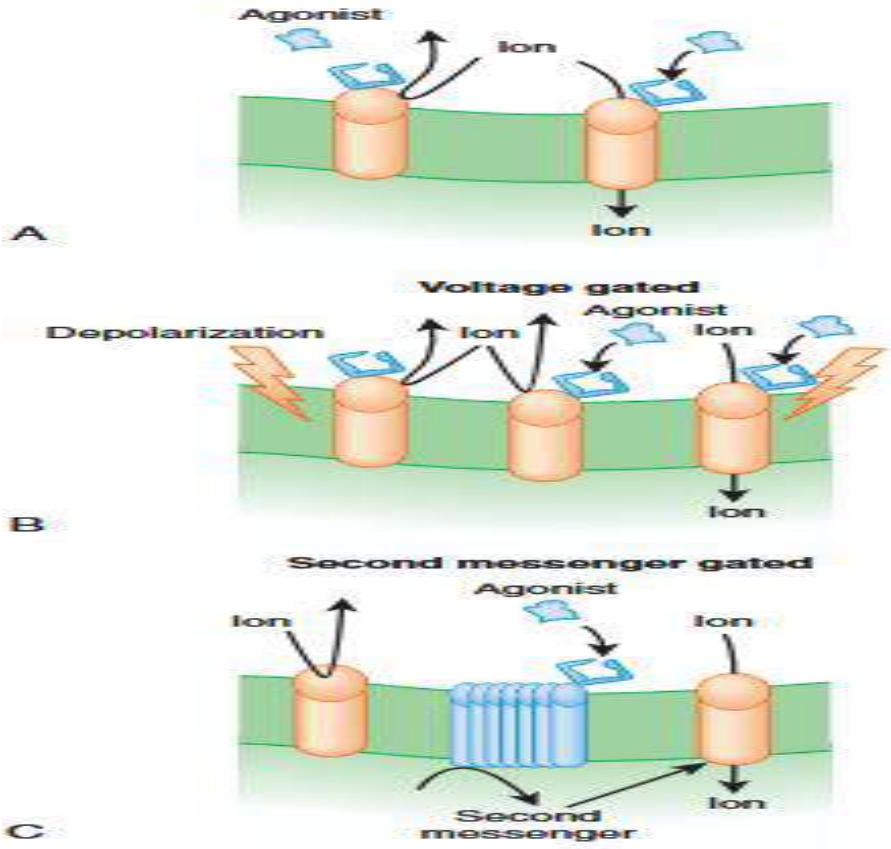

Figure 15 : Receptor-coupled transmembrane ion channels. **A:** Ligand gated or receptor-operated channel. **B:** Voltage gated channel. **C:** Second messenger gated channel (Bardal et al., 2011).

4.3. Kinase-linked and related receptors or transmembrane enzyme-linked receptors:

Also called Metabophores, these receptors span the cell membrane once only and are composed of an external binding site and an internal enzymatic component (Dick, 2011 ; Toutain, 2018). Although kinase enzymes predominate this class, these molecules include the receptor tyrosine kinases such as the epidermal growth factor and insulin receptors, receptor serinethreonine kinases such as the TGF-β receptor, and receptors linked to other enzyme activities such as the receptors for natriuretic pepides (Blumenthal and Garisson, 2011).

Tyrosine kinase enzymes can transfer a phosphate group from ATP to a tyrosine residue in an intracellular protein to increase its phosphorylation (figure 16). Protein

phosphorylation is one of the underlying mechanisms regulating protein function, similar to an on/off switch. It can alter the biological properties or the interaction of proteins with other proteins or peptides (Toutain, 2018).

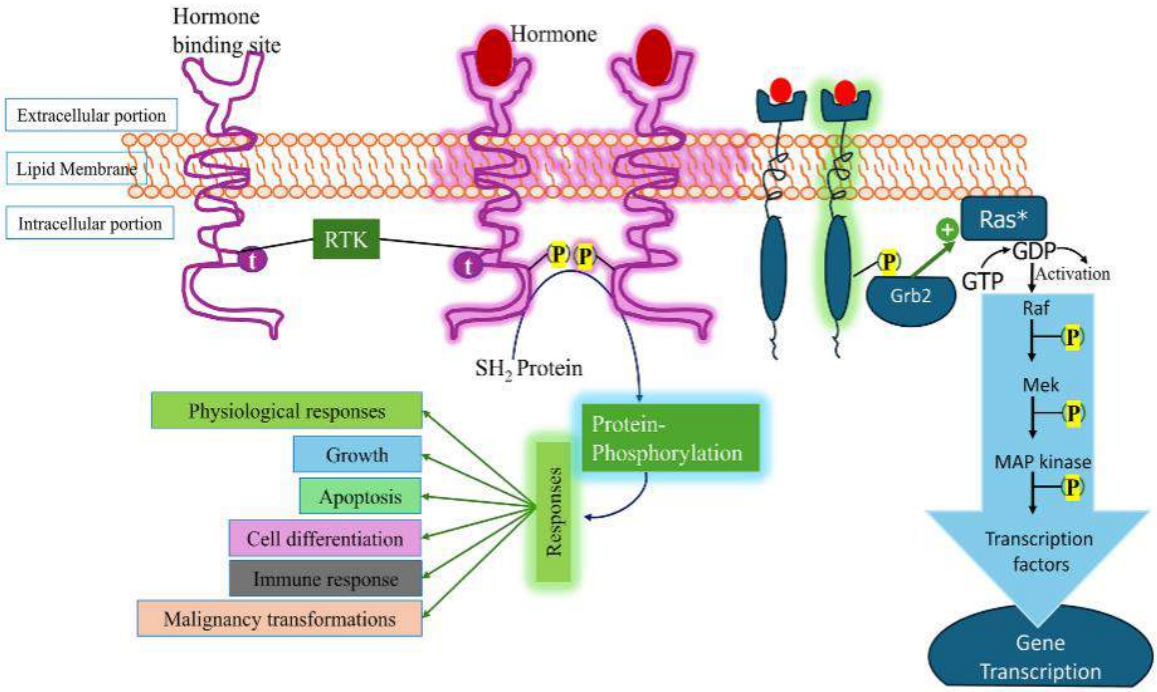

Figure 16: Signaling transduction mechanism of Receptor tyrosine kinase (Kamepalli et al., 2025).

4.4. Nuclear or gene expression receptors:

Nuclear receptors (NRs) are a class of ligand-activated transcription factors that sense certain molecules, such as steroids, thyroid hormones and vitamins, to directly bind DNA and modulate gene expression, bypassing the need for cytoplasmic signal cascades that mediate surface receptor and nuclear transcription mechanisms (Poreba and Durzynska, 2020). The typical structure of a nuclear receptor consists of a hinge region, a conserved ligand-binding domain and a DNA-binding domain. While some nuclear receptors are physically connected to chromatin, others remain in the cytoplasm until ligand interactions allow nuclear entry (Jin et al., 2025).

Lipophilic drugs passively cross the cell membrane and thus do not require cell membrane receptors. Steroid hormone receptors represent the typical intracellular

receptor, which includes estrogen receptor, androgen receptor, vitamin D receptor, retinoic acid receptor, glucocorticoid receptor, and thyroid hormone receptor (Ruby, 2026). After binding, the agonist-receptor complex diffuses to DNA, where it binds to DNA binding elements. Via this mechanism drugs act directly or through recruitment of coactivators or co-repressors (figure 17), which increase or decrease transcription of RNA to ultimately change protein expression (Bardal et al., 2011).

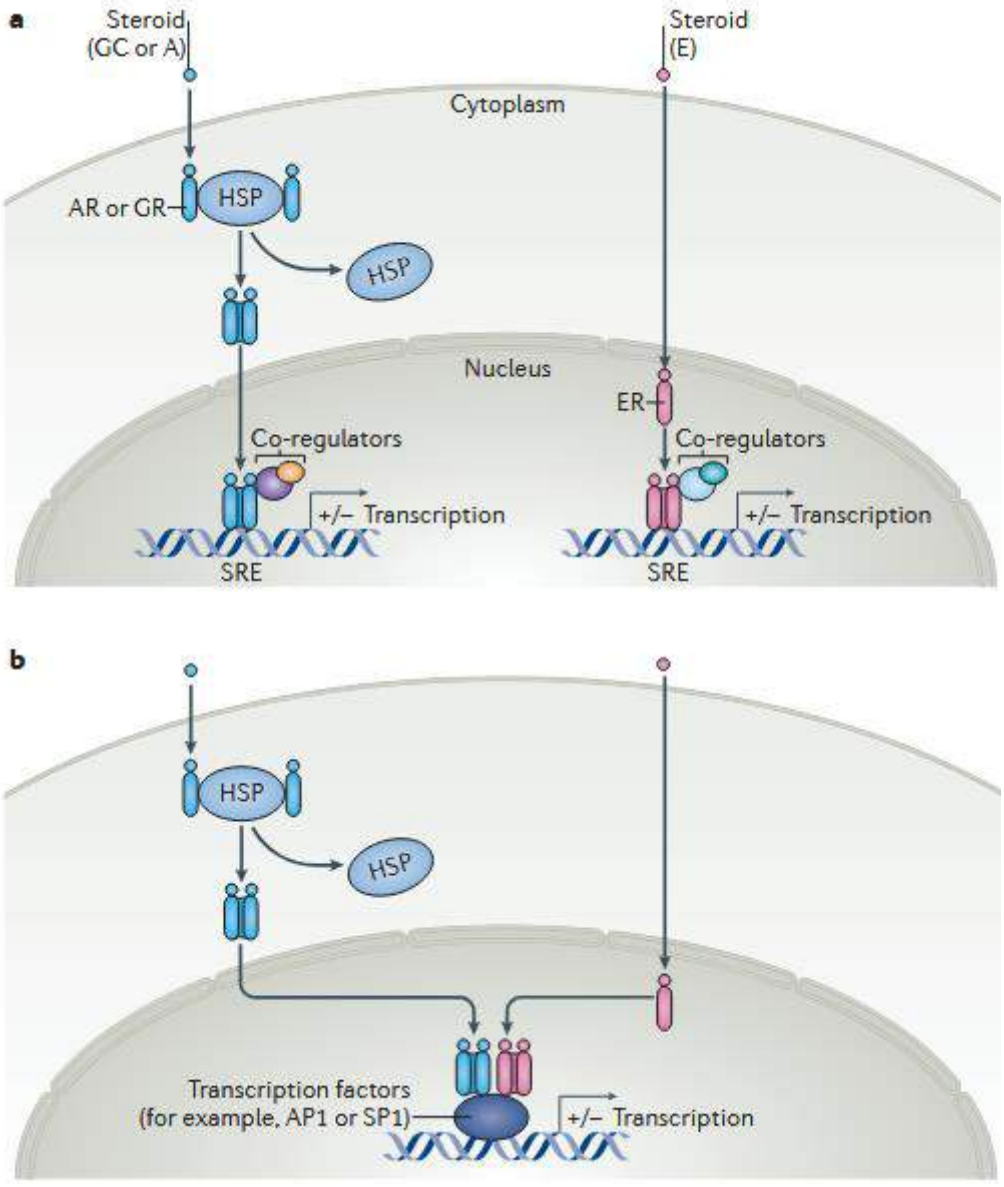

Figure 17 : Nuclear steroid signalling. **a** | Classic steroid signalling pathway. (GC : glucocorticoid ; A : androgen ; R: receptors ; HSPs : heat shock proteins ; E : oestrogen)

In the case of GC and A, steroid binding to cytoplasmic receptors triggers release from the HSPs, receptor dimerization, alterations in receptor conformation and nuclear localization. In the case of E, the sex steroid binds to nuclear receptors to promote dimerization and changes in receptor conformation. In all cases, nuclear dimerized receptors then bind to specific steroid-response elements (SREs) and interact with various co-regulators to modulate gene transcription through either repression or activation. **b** | Tethered steroid signalling. Nuclear steroid receptors can also modulate gene expression without direct DNA binding. In this case, they bind to other transcription factors, such as AP1 or SP1, to either repress or activate transcription (Levin and Hammes, 2016).

5. Duration of action:

The pharmacologic effect can also be confirmed by the duration of time that the drug-receptor complex sticks at, and they can also be said as residence time. The period of the drug-receptor complex is affected by vibrant processes which control the rate of drug association and dissociation from the target. A longer residence time elucidates a prolonged pharmacological effect. Longer residence time can be a possible drawback when it prolongs a drug's toxicity. For particular receptors, transient drug occupancy produces the desired pharmacologic effect, although prolonged occupancy causes toxicity (Thirumalai et al., 2021).

6. Receptors regulation:

The effect of a drug often diminishes when it is given repeatedly. The term used to describe a gradual decrease in responsiveness to chronic drug administration (days, months) is tolerance, whereas, tachyphylaxis is an acute form of tolerance (Toutain, 2018).

The receptors in a biological organism are not static and are consistently being altered to reflect and adjust to increased stimulation. Receptors are able to regulate their own expression through changes in synthesis and degradation, which are often mediated

by the same signaling proteins in a type of feedback regulation. Actual changes in the number of receptors expressed by a cell or a tissue are dependent on the time for either transcription and translation of new receptors (***upregulation***) or protein degradation (***downregulation***) (Ruby, 2026).

6.1. Up-regulation:

It is seen whenever a normally present receptor agonist decreases at a receptor zone below some point. After up-regulation, a cell becomes hypersensitive to the receptor agonist. So, any sudden release or application of a receptor agonist to a highly up-regulated zone can lead to overstimulation and potential cell injury or death (Dick, 2011).

6.2. Down-regulation:

In some cases, chronic administration of a drug causes a *down-regulation* or *desensitization* of receptors that can require dose adjustments to maintain adequate therapy (Blumenthal and Garisson, 2011). Receptor internalization, receptor degradation, and changes in transcription and translation may contribute to reduction in the quantity of receptor molecules on the cell surface (Bardal et al., 2011). The sequestration of receptors or redistribution from the plasma membrane to intracellular vesicles via endocytosis involves dephosphorylation of the receptor (figure 18). In another way, cytosolic proteins, such us arrestin and phosphodiesterase can bind to the intracellular portion of the receptor and uncouple signaling (Ruby, 2026).

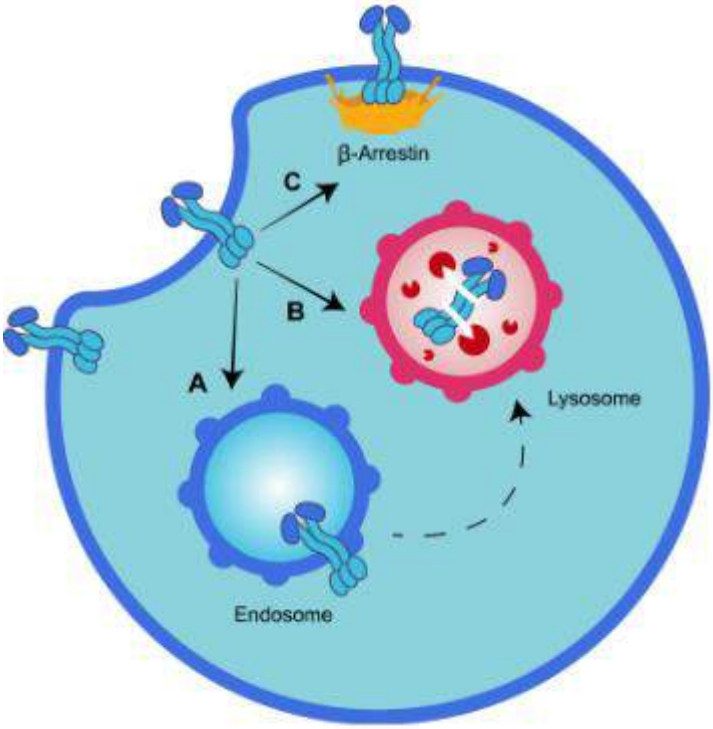

Figure 18: Receptor Regulation Mechanisms. **A**: Endocytosis and internalization within vesicles. **B**: Degradation of internalized receptors. **C**: Signal inhibition (Ruby, 2026).

7. Dose-response relationships:

Ultimately, to make informed clinical decisions regarding drug treatment, it is necessary to understand the relationship between the amount of drug given and the anticipated effect in the patient (Bardal et al., 2011). Increases in the dose produce increases in the response. Example: progressive increases in epinephrine dose produce increases in cardiac output and vasoconstriction, which lead to increases in blood pressure (Hsu and Martin, 2008). This relationship is described quantitatively by a hyperbolic dose-response curve (figure 19) according to the following equation :

$$E = \frac{Emax \times C}{C + EC50}$$

where E is the effect observed at concentration C, E_{max} is the maximal response that can be produced by the drug, and EC_{50} is the concentration of drug that produces 50% of maximal effect (Katzung, 2021).

Dose-response data are often presented as a plot of the drug effect (ordinate) against the logarithm of the dose or concentration (abscissa), transforming the hyperbolic curve into a sigmoid curve with a linear midportion (Katzung, 2021).

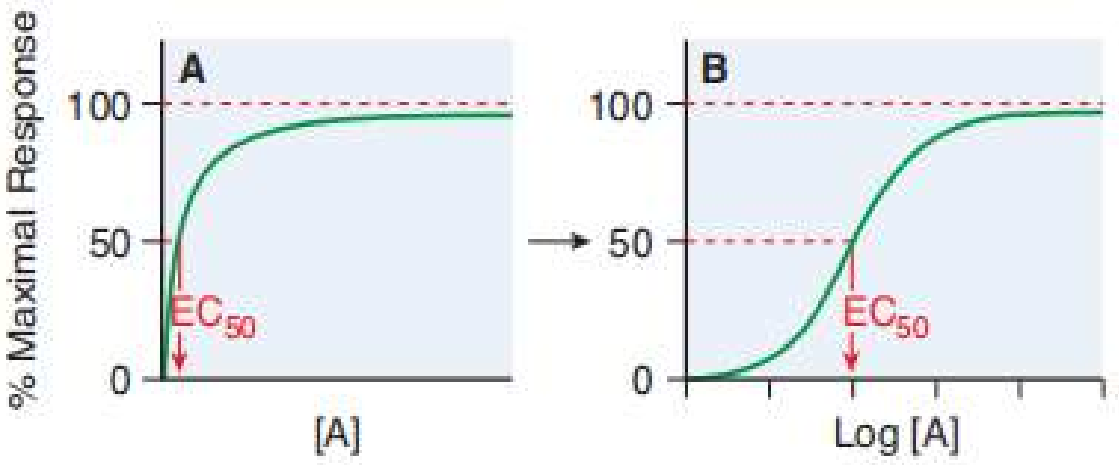

Figure 19: Dose-response curve (Blumenthal and Garisson, 2011).

The doses that produce a measurable effect, or effective doses, are in practice situated between the threshold dose and the dose that produces the maximum effect (for the substance in question). Mathematically, this range is zero and infinity, which explains why their determination is approximate or arbitrary (for example, the threshold dose is taken to be the dose that produces a certain percentage of the maximum effect). The dose that produces 50% of the maximum effect is the effective dose 50 (ED_{50}) or effective concentration (EC_{50}); it corresponds to the inflection point of the sigmoid curve in semi-logarithmic coordinates (Dangoumau et al., 2006 ; Ruby, 2026).

There are two basic types of dose-response curves: ***graded*** and ***quantal*** and each provides useful information for therapeutic decisions.

7.1. Graded dose-response curve : four main parameters describe it (figure 20):

- **Potency** refers to the dose (concentration) of a drug needed to produce the effect. The smaller the dose to produce the effect, the greater the potency.

- **Slope:** a useful parameter - when it is shallow, it suggests a greater chance of overlap between desired effects and side-effects, whereas a slope which is too steep suggests that it will be difficult to achieve precise control of the effects.

- **Efficacy** is a pharmacologic parameter used to describe a drug's ability to initiate and produce its maximal biological effect (Emax).

- **Variability** in the response can be expected from a specific dose and variation in dosage may be required to produce a given response (Hsu and Martin, 2008).

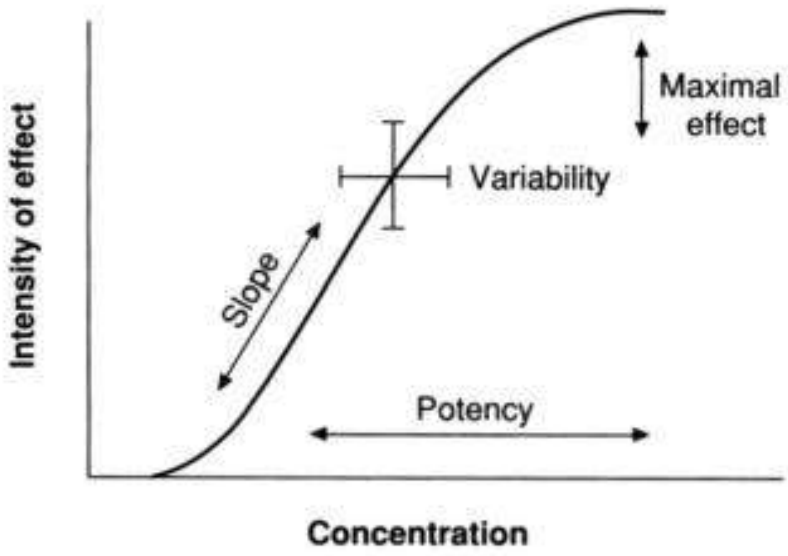

Figure 20 : The log dose–effect relationship, showing the four characteristic variables (Hsu and Martin, 2008).

The graded dose–response curves of three different hypothetical drugs are represented in figure 21(A). Drug A is more potent than Drug B or Drug C, whereas Drugs B and C have equal potency. Potency is sometimes used incorrectly as a measure of therapeutic effectiveness. In fact, in most cases potency is secondary to Emax in drug selection. However, in situations in which the absorption of drug is very poor, such that only small quantities of the drug reach the target, potency can be a critical

consideration. Drugs with higher Emax values have higher pharmacologic efficacy (Bardal et al., 2011).

7.2. Quantal dose-response curve:

A quantal dose–response curve best describes a binary or all-or-none response in relationship to a drug's dose in a population of subjects. The assumption is made that individual animals respond to the maximum possible or not at all. Thus, dose is not expressed as to the intensity of the effect but to the frequency with which any dose produced the all-or-none response (Hsu and Martin, 2008).

Quantal dose–response relationships are used to establish the useful drug effect and the toxic (death) drug effect curves. The dose of the drug that elicits a response at the median effective dose concentration in 50% of a population is known as ED_{50} (figure 21(B)). The median toxic dose (TD_{50}) defines the dose where 50% of a population experiences a toxic response, and if that response is lethal, a median lethal dose (LD_{50}) can also be established (Ruby, 2026).

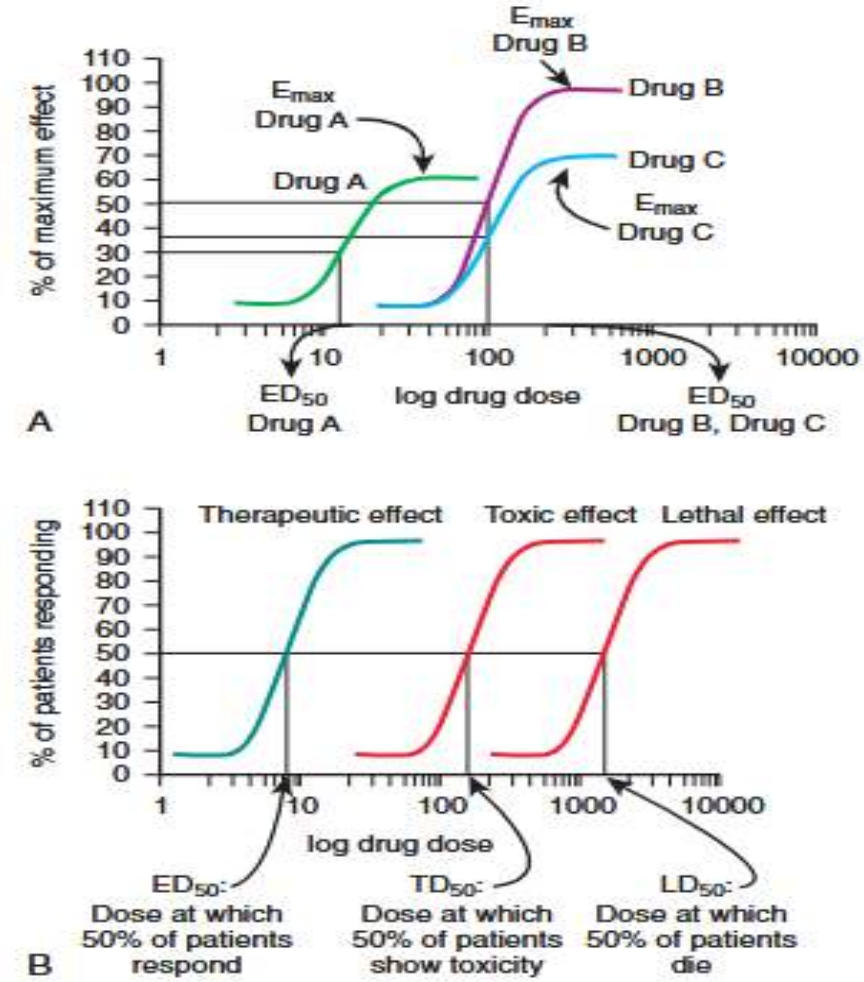

Figure 21 : A. Graded dose-response curve, B. Quantal dose-response curve (Bardal et al., 2011).

Therapeutic index is a ratio used to evaluate the safety of the drug. It can be calculated according to the following equation:

$$TI = \frac{\text{LD50}}{\text{ED50}}$$

Theoretically, the drugs are used safely if they have a large TI (Hsu and Martin, 2008). Therapeutic window is a loosely defined term that generally refers to the range of doses that produce therapeutic effects with minimal toxic effects. However, the standard safety margin is defined as the percentage increase of a dose above the therapeutic dose that is toxic or lethal to a given proportion of subjects

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