**Dose–response relationships**

- Agonist drugs mimic the action of the original endogenous ligand for the receptor.
- The magnitude of the drug effect depends on the drug concentration at the receptor site, which, in turn, is determined by both the dose of drug administered and by the drug’s pharmacokinetic profile, such as rate of absorption, distribution, metabolism, and elimination.
These relations are exhibited as following:

A. Graded dose–response relationships (individual):

The response is a graded effect, meaning that the response is continuous and gradual.

B. Quantal dose–response relationships (population)

describes an all-or-no response
Relation between Drug Dose & Clinical Response

- In order to make rational therapeutic decisions, the prescriber must understand how drug-receptor interactions underlie
  
1. The relations between **dose and response** in patients

2. The nature and causes of **variation in pharmacologic responsiveness**

3. The clinical implications of **selectivity of drug action**.
A. Graded dose–response relationships

- The magnitude of the drug effect depends on the drug concentration at the receptor site, which in turn is determined by the dose of drug administered and by factors characteristic of the drug pharmacokinetic profile, such as rate of absorption, distribution, and metabolism.

- As the concentration of a drug increases, the magnitude of its pharmacologic effect also increases.

- Plotting the magnitude of the response against increasing doses of a drug produces a graph, the graded dose–response curve.

- Two important properties of drugs, can be determined by graded dose–response curves which are:

1. Potency
2. Efficacy
1. Potency:

- A measure of the amount of drug necessary to produce an effect of a given magnitude.
- The concentration of drug producing an effect that is 50 percent of the maximum is used to determine potency and is commonly designated as the $\text{EC}_{50}$.
- Drug A is more potent than Drug B, because a lesser amount of Drug A is needed when compared to Drug B to obtain 50-percent effect.
Potency is affected by:

1. Receptor concentration or density in tissue.

2. Efficiency of stimulus-response coupling mechanism in tissue.

3. Affinity: the strength of the interaction (binding) between a ligand and its receptor.

4. Efficacy

Potent drugs are those which elicit a response by binding to a critical number of a particular receptor type at low concentrations (high affinity) compared with other drugs acting on the same system and having lower affinity and thus requiring more drug to bind to the same number of receptors.
2. Efficacy

- It is the ability of a drug to elicit a response when it interacts with a receptor.

- Efficacy is dependent on:
  1. Number of drug–receptor complexes formed
  2. The efficiency of the coupling of receptor activation to cellular responses.

- A drug with greater efficacy is more therapeutically beneficial than one that is more potent.

- Maximal efficacy (Emax) of a drug assumes that all receptors are occupied by the drug, and no increase in response will be observed if more drugs are added.

- The height of maximal response is used to measure maximal efficacy of agonist drug, and to compare efficacy of similar acting agonists.
Effect of drug concentration on receptor binding

- The quantitative relationship between drug concentration and receptor occupancy is expressed as follows:

  \[
  \text{Drug} + \text{Receptor} \quad \leftrightarrow \quad \text{Drug–receptor complex} \quad \rightarrow \quad \text{Biologic effect}
  \]

  ➢ As the concentration of free drug increases, the ratio of the concentrations of bound receptors to total receptors approaches unity.
Concept of drug receptor binding & agonists

A receptor can exist in at least two conformational states, active ($R_a$), and inactive ($R_i$). These states are in equilibrium, & the inactive state $R_i$ predominates in absence of agonist drug, thus basal activity will be low or absent.

If a drug that has a higher affinity for $R_a$ than $R_i$ is given, it will drive the equilibrium in favor of active state and thus activate more receptors.

- **Such drug will be an agonist.**

  A full or strong agonist is sufficiently selective for the active conformation that at a high concentration it will drive the receptors completely to the active state.
• If a different but structurally similar compound binds to the same site on $R$ but with only slightly or moderately greater affinity for $R_a$ than for $R_i$, its effect will be less, even at high concentrations.

• Such a drug that has intermediate or low efficacy is referred to as a partial agonist.
Intrinsic Activity

• An agonist binds to a receptor and produces a biologic response based on the concentration of the agonist and the fraction of activated receptors.

• The intrinsic activity of a drug determines its ability to fully or partially activate the receptors.

• Drugs may be categorized according to their intrinsic activity and resulting Emax values.
A. Full agonists

• If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is a full agonist.

• Full agonists bind to a receptor, stabilizing the receptor in its active state and are said to have an intrinsic activity of one.

• All full agonists for a receptor population should produce the same $E_{\text{max}}$.

• As this brief description illustrates, an agonist may have many measurable effects, including actions on intracellular molecules, cells, tissues, and intact organisms.

• All of these actions are attributable to interaction of the drug with the receptor.

• For full agonists, the dose–response curves for receptor binding and each of the biological responses should be comparable.
B. Partial agonists

- Partial agonists have intrinsic activities greater than zero but less than one
- Even if all the receptors are occupied, partial agonists cannot produce the same Emax as a full agonist.
- Partial agonist may have an affinity that is greater than, less than, or equivalent to that of a full agonist.
- When a receptor is exposed to both a partial agonist and a full agonist, the partial agonist may act as an antagonist of the full agonist.
- Consider what would happen to the Emax of a receptor saturated with an agonist in the presence of increasing concentrations of a partial agonist.
- As the number of receptors occupied by the partial agonist increases, the Emax would decrease until it reached the Emax of the partial agonist.
- This potential of partial agonists to act as both an agonist and antagonist may be therapeutically utilized.
C. Inverse agonists

• Typically, unbound receptors are inactive and require interaction with an agonist to assume an active conformation.

• Some receptors show a spontaneous conversion from $R$ to $R^*$ in the absence of an agonist.

• Inverse agonists, unlike full agonists, stabilize the inactive $R$ form and cause $R^*$ to convert to $R$.

• This decreases the number of activated receptors to below that observed in the absence of drug.

• Inverse agonists have an intrinsic activity less than zero, reverse the activity of receptors, and exert the opposite pharmacological effect of agonists.
A full agonist produces complete activation of a receptor at high drug concentrations.

Partial agonist binding results in less than 100% activation, even at very high concentrations.

Inverse agonists produce a response below the baseline response measured in the absence of drug.

In this example, approximately 12% of the receptors show constitutive activity in the absence of agonist.
ANTAGONISTS

They are of 3 main types:

1. Chemical antagonist:

   - This combines with agonist and inactivates it away from tissues or receptors

Examples:

a. Alkaline antacids neutralize HCl in stomach of peptic ulcer patients;

b. Protamine (basic) neutralizes the anti-coagulant heparin (acidic) in plasma

c. Chelating agents bind with higher affinity to heavy metals (e.g. lead, mercury, arsenic) in plasma and tissues, preventing their tissue toxicity
2. Physiological antagonist:

- This is actually an agonist on the same tissue but produces opposite effect to that of the specific agonist; it acts by mechanisms or receptors that are different from those of the specific agonist.

- Physiological antagonists quickly reverse the action of the specific agonist on the same tissue.

Examples:

Adrenaline, given IM, is a quick acting physiologic antagonist to histamine (that is released from mast cells or basophils) in anaphylactic shock; it is a life-saving drug in this condition.
3. Pharmacological antagonist:

- **Pharmacological receptor antagonists** have affinity for the receptors but have *no intrinsic activity* or efficacy.

There are three main types:

**A. Competitive reversible antagonist:**

This antagonist, because of *similarity in its chemical structure to agonist*, competes with agonist for binding to its specific receptors in tissue, and thus decreases or prevents binding of agonist and its effect on tissue.

The antagonist molecules bind to the agonist receptors with *reversible ionic bonds*, so that *it can be displaced competitively from receptors* by increasing the concentration or dose of agonist, and thus *response of tissue to agonist is restored.*
The DR curve of agonist is shifted to the right, and the maximal response can be restored by increasing dose of agonist. The more is the concentration of antagonist, the greater is this shift of DR curve of agonist to the right.

**Examples:**
- atropine is a competitive reversible antagonist to Ach at muscarinic receptors;
- Beta-blockers are competitive antagonists to adrenaline at beta–adrenergic receptors.
B. Non-competitive antagonist:

There are two subtypes:

1. Irreversible antagonist:

Here, the antagonist molecules either bind to agonist receptors by strong irreversible covalent bonds or dissociate very slowly from the receptors, so that the effect of antagonist can not be overcome fully by increasing concentration of agonist.
The dose response curve of agonist is shifted slightly to the right, but the maximal height or response of curve is depressed and can NOT be restored by increasing the dose of agonist. This is due to decrease in number of receptors remaining available to bind to agonist.

The more is the concentration of antagonist, the more is depression of maximal response.
2. Allosteric antagonism:

Here, the antagonist binds to allosteric site on receptor that is different from the site that binds agonist molecules, leading to change in receptor binding or affinity to agonist with subsequent antagonism.

The dose response curve of antagonist is similar to that of irreversible non-competitive antagonist.

Note: Allosteric enhancement: with some receptors, a drug can bind to another allosteric site on agonist receptor leading to increase in binding of agonist to its receptor and thus allosteric enhancement of agonist effect. E.g. Binding of benzodiazepines to GABA-A receptors can enhance the depressant GABA effect on brain neurons.
Receptor regulation

1. Receptor up-regulation:
This means increase in number of receptors and/or affinity of specific receptors (receptor supersensitivity).

It may occur with:

A. Prolonged use of receptor antagonist: here, there is lack of binding of receptor to agonist for long period of time

B. Disease: e.g. hyperthyroidism: here excess thyroxine hormone in blood stimulate proliferation of beta-adrenergic receptors in heart which increases risk of cardiac arrhythmia from adrenaline or use of beta-adrenoceptor agonists.
B. Receptor down-regulation (Receptor tolerance):

- This means a decrease in number and/or affinity of available specific receptors due to their prolonged occupation by agonist.

- It occurs with continued use (for days or weeks) of receptor agonist, and is evident as decrease in response to agonist.

- In order to restore the intensity of response, the dose of agonist must be increased.

**Tachyphylaxis:** it is a rapidly developing receptor tolerance

- It is not due to receptor down-regulation

- It is associated with repeated use of large doses of direct receptor agonist, usually at short dose intervals, OR with continuous IV infusion of agonist.
It may be due to:

1. **Desensitization of receptors:**
   
   *Change in the receptor:* where the agonist-induced changes in receptor conformation result in receptor phosphorylation, which diminishes the ability of the receptor to interact with G proteins.

2. **Depletion of intra-cellular stores of transmitter**
   
   *e.g.* depletion of noradrenaline stores in vesicles inside sympathetic nerve ending resulting from repeated use of indirect sympathomimetic amphetamine.

In order to restore the response, the agonist drug must be stopped for short time to allow for recovery of receptors or stores of transmitter.