

Basic concepts and processes in Pharmacology

Pharmacodynamics: derived from two Greek words: **Pharmakon** = “ Drug”
dynamics = “change” (drug action)

Pharmacodynamics is defined as the study of the biochemical and physiologic effects of drugs and the molecular mechanisms by which those effects are produced.

In short, pharmacodynamics is the study of what drugs do to the body and how they do it.

Drug action is the mechanism by which drug exerts its effects.

Drug effect is the biochemical or physiological changes result from drug action – drug responses or effects observed when the drug is administered.

E.g., drug act on vascular smooth muscle and cause relaxation (drug action) → cause vasodilation and hypotension (drug effects).

Mechanism of drug action:

- 1) Most of the drugs act by interacting with a cellular component called receptor –
Receptor drug interactions

These drugs act on the body by altering cellular function. A drug can modify cell function or rate of function, but it cannot impart a new function to a cell or to a target "drugs can only alter the rate of pre-existing processes".

- 2) Some drugs act through simple physical or chemical reactions – **Non receptor – drug interactions:**

These drugs produce their therapeutic effects on the body by changing the cellular environment through nonspecific chemical or physical interactions without receptor interactions include changes in osmotic pressures, lubrication or PH. Common examples include antacids. Antacids neutralize gastric acidity by direct chemical interaction with stomach acid.

- 3) **Interference with ion channels** – some drug act directly on ion channels and alters their function. E.g., local anesthesia act by block Na^+ channels
- 4) **Alteration of the enzymes activity.** e.g., inhibition of angiotensin converting enzyme by Captopril drug.
- 5) **Antimetabolic action** in which the drug interferes with normal metabolic process – acting as a nonfunctional analogue of a naturally occurring metabolite. e.g., sulfonamide "antibacterial drug" cause inhibition of bacterial enzyme that responsible for folic acid synthesis lead to bacterial death.
- 6) **Carrier mechanism:** drugs act by interfering with passage of molecules across the cell membrane, e.g., inhibition of noradrenaline uptake by tricyclic antidepressant drug.
- 7) **Incorporated into cellular constituents** – some drugs that are structurally similar to nutrients (e.g., purines, pyrimidines) required by body cells and that can be interfere with normal cell functioning. Several anticancer drugs act by this mechanism.

Drug-Receptor interactions:

Receptors: are any functional macromolecules in a cell to which a drug binds to produce its effects.

Receptors naturally occurring macromolecules that mediate the effects of endogenous physiologic substances such as neurotransmitters and hormones. E.g., histamine receptor occupied by histamine and cholinergic receptor by acetyl choline.

Receptors may be found on membrane, within membrane, on inner surface of membrane, in cytoplasm, or in nucleus, and may be a chemical, a protein on a cell or in blood or tissue spaces, or on a bacteria or virus.

The initial step leading to a response is – Drug must bind to its specific target site at receptor. Followed by a sequence of events that result in response.

Drug (Ligand) + Receptor \leftrightarrow Drug–receptor complex \rightarrow Biologic effect \rightarrow Response

Affinity: strength of the attraction between a drug and its receptor. Drugs with high affinity are strongly attracted to their receptors. Conversely, drugs with low affinity are weakly attracted.

Intrinsic activity: the ability of a drug to activate the receptor following binding. The drug with high intrinsic activity cause intense receptor activation. Conversely, the drug with low intrinsic activity cause only slight activation. The intrinsic activity of a drug is reflected in its **maximum efficacy**.

Drugs with high intrinsic activity have high maximal efficacy. That is, by causing intense receptor activation, they are able to cause intense responses. Conversely, if intrinsic activity is low, maximal efficacy will be low as well.

When drugs bind to receptors they can do one of two things: they can either mimic the action of endogenous regulatory molecules called agonists or they can block the action of endogenous regulatory molecules called antagonists.

Agonists: are drugs that bind with a receptor to produce a therapeutic response (activate receptors). Agonists may accelerate or slow normal cellular processes, depending on the type of receptor activated.

E.g., epinephrine-like drugs act on the heart to increase the heart rate, and acetylcholine-like drugs act on the heart to slow the heart rate; both are agonists.

Agonists have two main properties:

- 1) **Affinity:** the ability of the agonist to “bind to” the receptor
- 2) **High intrinsic activity** or Efficacy: the ability to cause a response via the receptor interaction

Full agonist: can elicit a maximal effect at a receptor.

Partial agonists also mimic the actions of endogenous regulatory molecules, but they produce responses of intermediate intensity – have only moderate intrinsic activity and reduced efficacy as compared with full agonist.

Antagonists: are drugs that bind with a receptor and produce their effects by block or preventing receptor activation by endogenous regulatory molecules and drugs.

Antagonists have:

- 1) **Affinity** for a receptor (can bind with receptors) but
- 2) **Little or no intrinsic activity**, (no efficacy).

Affinity allows the antagonist to bind to receptor but lack intrinsic activity prevents the bound antagonist from causing receptor activation.

E.g., Antihistamines, suppress allergic symptoms by binding to histamine receptors and prevent the activation of these receptors by histamine – that released in response to allergens.

Antagonists can be subdivided into two major classes:

1. **Noncompetitive antagonists:** antagonists bind irreversibly to receptors → reducing the total number of receptors available for activation by an agonist, thereby reducing the maximal response that an agonist can elicit. If sufficient antagonist is present, agonist effects will be blocked completely.

2. **Competitive antagonists:** (Most antagonists are competitive)

Antagonists bind reversibly to receptors → produce receptor blockade by competing with agonists for receptor binding.

**If an agonist and a competitive antagonist have equal affinity for a particular receptor, then the receptor will be occupied by whichever agent—agonist or antagonist—is present in the highest concentration.

**If there are more antagonist molecules present than agonist molecules, antagonist molecules will occupy the receptors and receptor activation will be blocked.

**In the presence of sufficiently high amounts of agonist, agonist molecules will occupy all receptors and inhibition will be completely overcome.

Receptors and selectivity of drug action

1. **Selective drug:** If a drug acts on specific receptors, it is said to be selective and can cause specific effects.

2. **Nonselective drug:** If a drug acts on a variety of receptors, it is said to be nonselective and can cause multiple and widespread effects.

Receptor Regulation: Receptors are dynamic cellular components that can be synthesized by body cells. In response to continuous activation or continuous inhibition, the number of receptors on the cell surface can change.

1. **Desensitization or receptor down-regulation:** Prolonged stimulation of cells with repeated or continuous agonist administration → usually reduces the number or sensitivity of receptors due to destruction of receptors by the cell and modification of receptors. As a result, the cell becomes less responsive to the agonist (a process called receptor desensitization or down-regulation). Some drugs when given continuously or repeatedly their effects or responses are gradually decreases.

When a patient develops a decreased response to a drug in very short time, we call it **Tachyphylaxis** or desensitization. When a patient develops a decreased response to a drug during several days or weeks, we call it **Tolerance**. The patient then requires larger doses to produce the same response.

2. **Receptor up-regulation:** Prolonged inhibition of normal cellular functions with an antagonist may increase receptor number or sensitivity "hypersensitive" due to

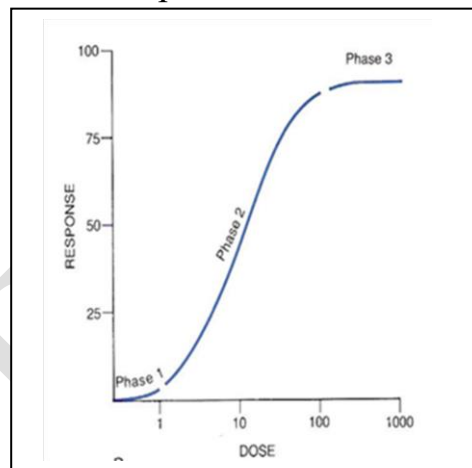
synthesis of more receptors (a process called receptor up-regulation). If the antagonist is suddenly reduced or stopped, the cell becomes excessively responsive to an agonist. These changes in receptors may explain why some drugs must be tapered in dosage and discontinued gradually.

Dose–Response curve

Dose-response curve represent relationships between the size of an administered dose and the intensity of the response produced. The dose-response relationship is a fundamental concern in therapeutics.

Dose-response curve determines:

- ✓ the minimum amount of drug that can be used
- ✓ the maximal response that drug can elicit
- ✓ how much you need to increase dosage to produce the desired response
- ✓ It's essential for successful drug therapy.



The most obvious and important characteristic revealed by these curves is that the dose-response relationship is graded.

The graded nature of the dose-response relationship is essential for successful drug therapy. That is, as the dosage increases, the response becomes progressively larger.

Because drug responses are graded, therapeutic effects can be adjusted to fit the needs of each patient. \Rightarrow all we need to do is raise or lower the dosage until a response of the desired intensity is achieved.

The dose-response relationship or curve has three phases.

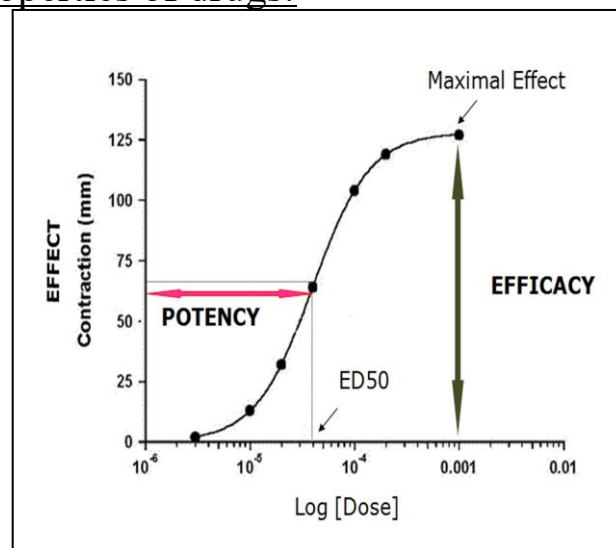
Phase 1, occur at low doses, the curve is relatively flat during this phase because doses are too low to elicit a measurable response.

During **phase 2**, an increase in dose elicits a corresponding increase in the response; it is during this phase that the dose-response relationship is graded. As the dose is raised higher, we eventually reached the point where \uparrow in dose is unable to elicit a further \uparrow in response. At this point, the curve flattens into **phase 3**.

Dose-response curves reveal two characteristic properties of drugs:

Maximal Efficacy is defined as the largest effect that a drug can produce. Maximal efficacy is indicated by the height of the dose-response curve.

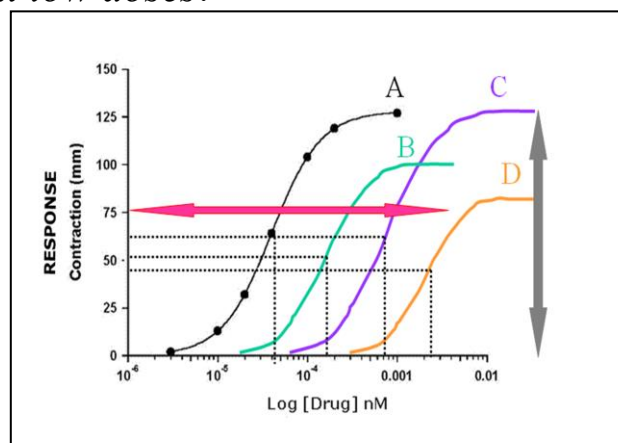
Relative Potency refer to the amount of drug we must give to elicit an effect. Potency is indicated by (dosage).



E.g. if Drug A causes a greater maximum intensity of response than Drug B (regardless of dose), $\Rightarrow\Rightarrow$ Drug A is more efficacious than Drug B
A potent drug is one that produces its effects at low doses.

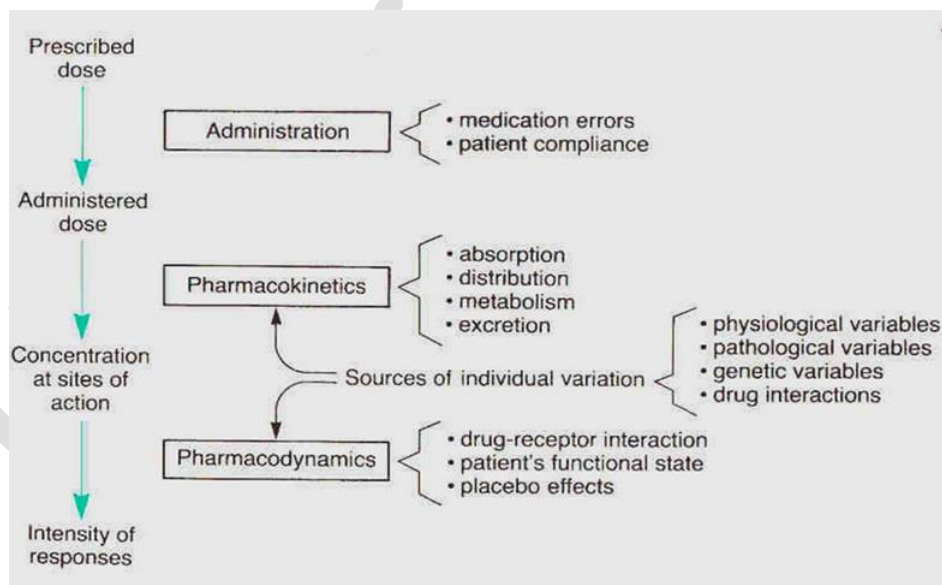
Rank order of efficacy: $A = C > B > D$

Rank order of potency: $A > C > B > D$



Factors that determine the intensity of drug responses

Multiple factors determine how an individual will respond to a prescribed dose of a particular drug



1. Administration

Dosage size, the route and the timing of administration are important determinants of drug responses. Accordingly, the prescribing clinician will consider these variables with care.

Unfortunately, drugs are not always administered as prescribed: **poor patient compliance and medication errors** by health care providers can result in major discrepancies between the dose that is prescribed and the dose that is actually administered. Such discrepancies can significantly alter the outcome of treatment. To help to minimize errors caused by poor patient compliance, you should give patients complete instruction about their medication and how to take it.

Medication errors made by health care providers may result in a drug being administered by the wrong route, in the wrong dose, or at the wrong time; the patient may even be

given the wrong drug. Any of these errors will detract from achieving the therapeutic objective.

2. Pharmacokinetics: 1) drug absorption 2) drug distribution 3) drug metabolism 4) drug excretion

3. Pharmacodynamics

Once a drug has reached its sites of action, pharmacodynamic processes determine the nature and intensity of the response.

- **Drug – receptor interaction:**
- **Patient's functional state** can influence pharmacodynamic processes. e.g., a patient who has developed tolerance to morphine will respond less to a particular dose than will a patient that lacks tolerance.
- **Placebo (psychological) effects** also help to determine the responses that a drug elicits.

“Placebo” is a drug dosage form, such as a tablet or capsule, that has no pharmacologic activity because it contains no active ingredients. When taken, the patient may report a therapeutic response. This response can be beneficial in patient's being treated for illnesses such as anxiety, because the patient tends to take fewer potentially habit-forming drugs

4. Individual Variations in Drug Responses: Variables that affect drug action

Many factors that can cause one patient respond to drugs differently than another. When you know these factors, you will be better prepared to reduce individual variation in drug responses, thereby maximizing the benefits of treatment and reducing potential for harm.

1) Physiological variables

Body weight and composition: Dosages must be adapted to size. The “body surface area” calculation is better than body weight because it takes into account weight as well as percentage of body fat.

Age: Infants very sensitive to drugs: due to organ immaturity and/or receptor numbers on cells – Elderly very sensitive to drugs-due to organ system degeneration (decreased metabolic inactivation and receptor number)

Gender: Response is different to same drug and dosage between men and women – due to hormonal differences, Some drug more effective in men, other more effective in women – Until recently, all drug research done in males

2) Pathological variables (especially diminished function of the kidneys and liver, the major organs of drug elimination)

3) Genetic variables: Genetic factors can alter the metabolism of drugs and can predispose the patient to unique drug reaction. Genetic variations can result in ↑or↓ metabolism of certain drugs.

4) Drug Interactions