Lecture 4

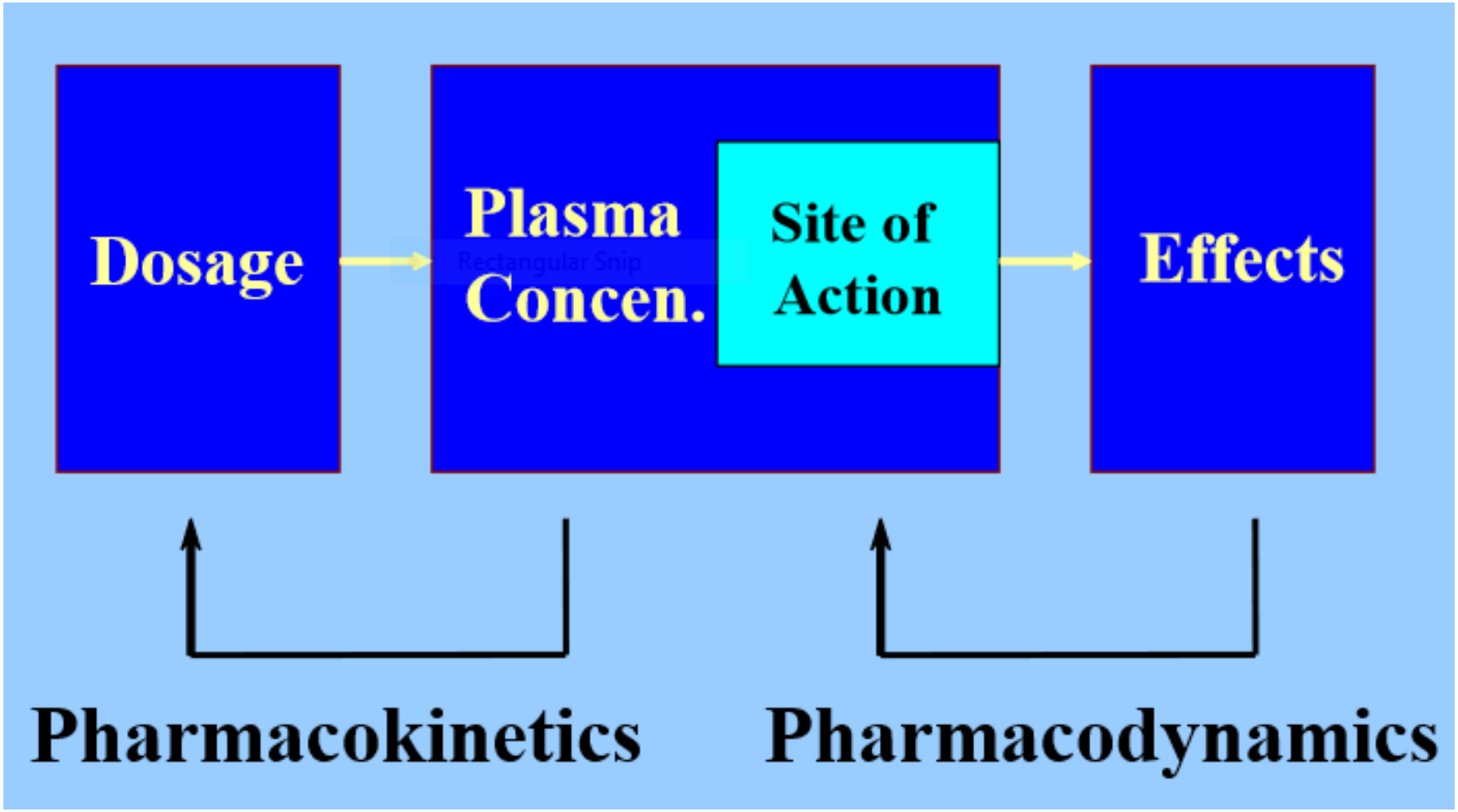
Basic concepts and processes in Pharmacology

- Pharmacodynamics: dose response relationships
- Adverse drug reactions
- Drug interactions: Drug – Drug and Drug – Food interactions

Objectives:

- Upon completion of this lecture, student will be able to answer the following questions:

1. Define the pharmacodynamics and discuss the mechanism of drug action.
2. Describe drug-receptor interactions
3. Discuss dose response relationships
4. Differentiate between maximal efficacy, potency, affinity, intrinsic activity, agonist and antagonist drugs
5. Differentiate between receptor down-regulation and receptor up-regulation
6. Define the types of adverse effects of drugs and describe the adverse effects of drugs in general.
7. Describe various drug interactions: Drug-drug interactions and Drug-food interactions


Dosage
Plasma Concen.
Site of Action
Effects
Pharmacokinetics
Pharmacodynamics

Pharmacodynamics

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

- **Mechanism of drug action**
- ***Non receptor – drug interactions:***
- Some 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, antiseptics, saline laxatives, and chelating agents.

- ***Drug-Receptor interactions:***
- Most 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".
- ***Receptors:*** are any functional macromolecules in a cell to which a drug binds to produce its effects.
- Receptors naturally occurring target 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.

Drug (Ligand)

+

Receptor

↕

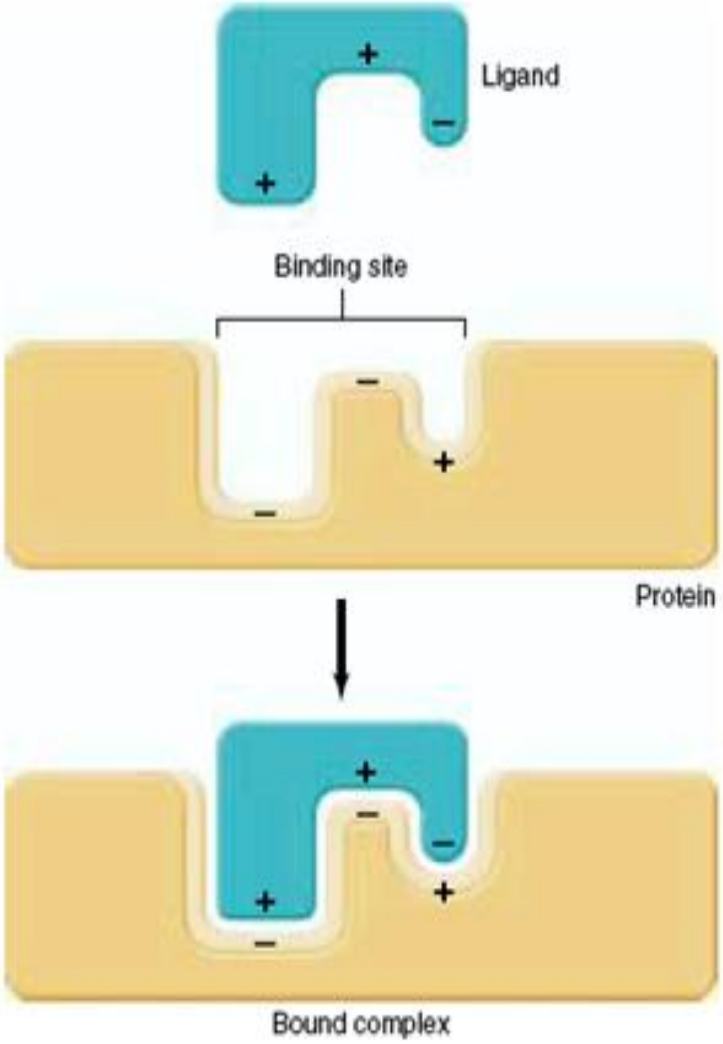
Drug–receptor complex

↓

Biologic effect

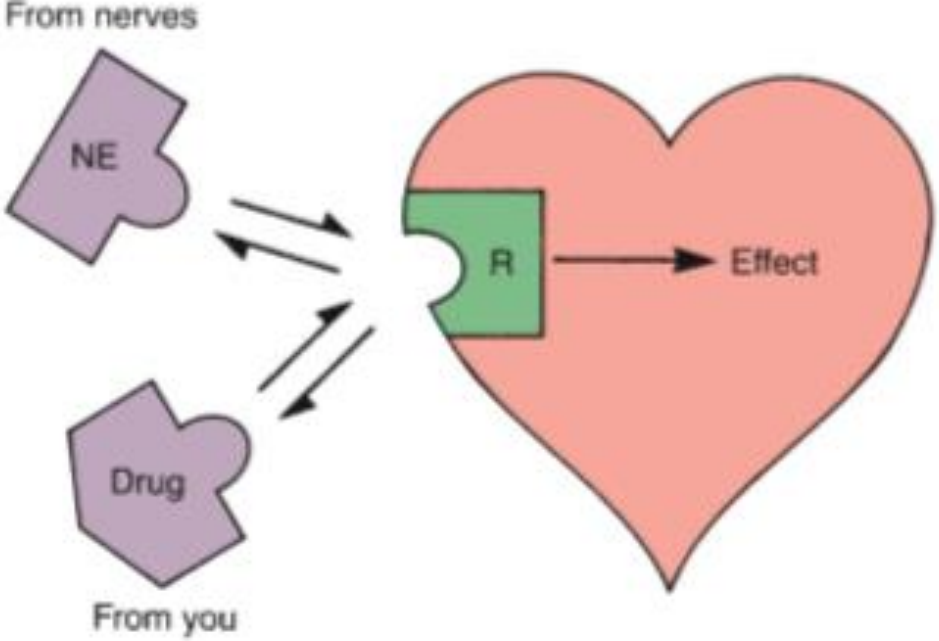
↓

RESPONSE



Drug–receptor complex initiates physiochemical reactions that stimulate or inhibit normal cellular functions.

The drug molecule has to be similar in size, shape, chemical structure to endogenous substances in order to combine to its specific receptors.



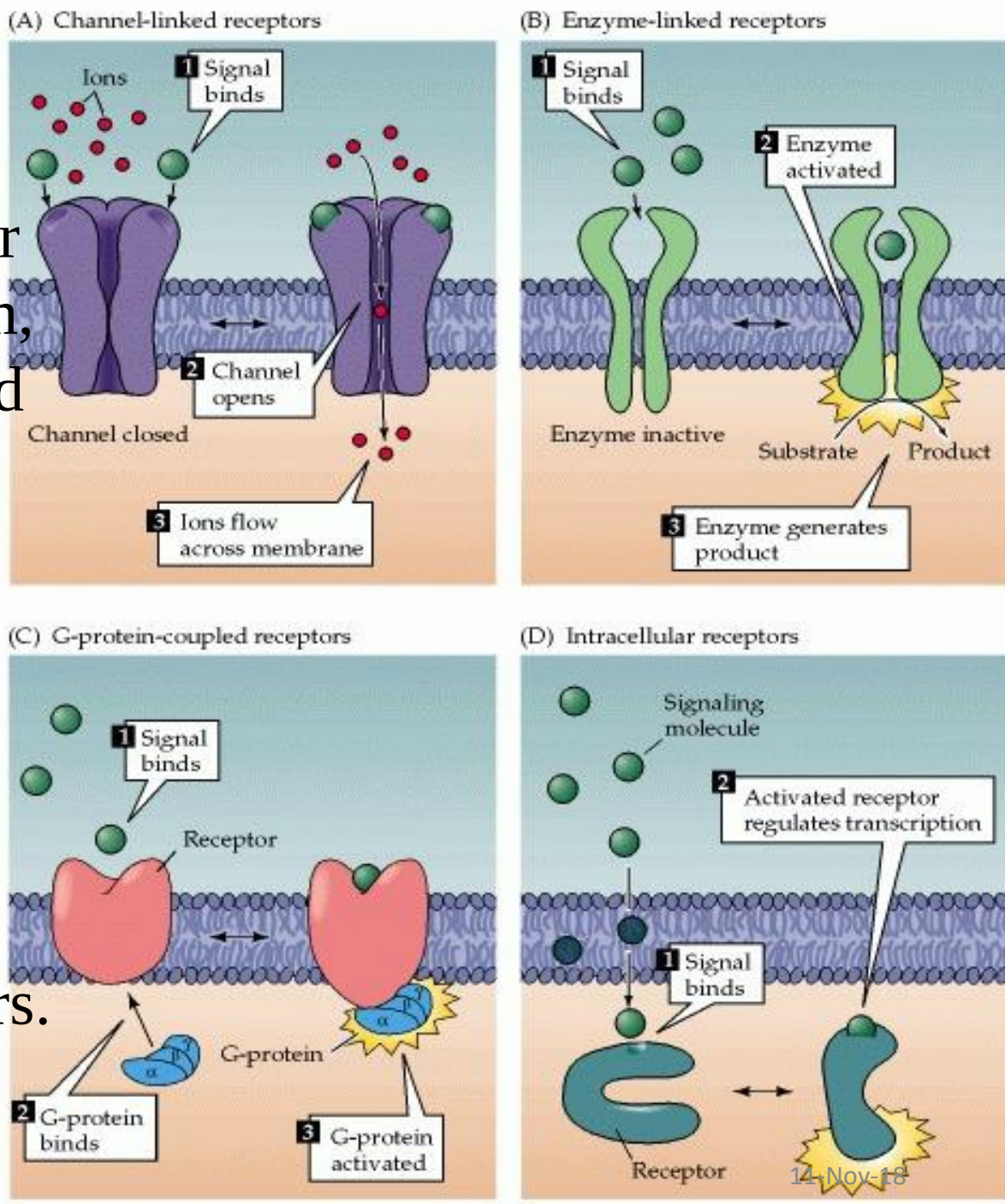
Interaction of drugs with receptors for norepinephrine.
Under physiologic conditions, cardiac output can be increased by the binding of norepinephrine (NE) to receptors (R) on the heart. Norepinephrine is supplied to these receptors by nerves. These same receptors can be acted on by drugs, which can either mimic the actions of endogenous NE (and thereby increase cardiac output) or block the actions of endogenous NE (and thereby reduce cardiac output).

Most receptors are named based on their endogenous ligands like serotonin receptors, acetylcholine receptors

Types of receptors

Based on their molecular structure and mechanism, receptors may be divided into four families:

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

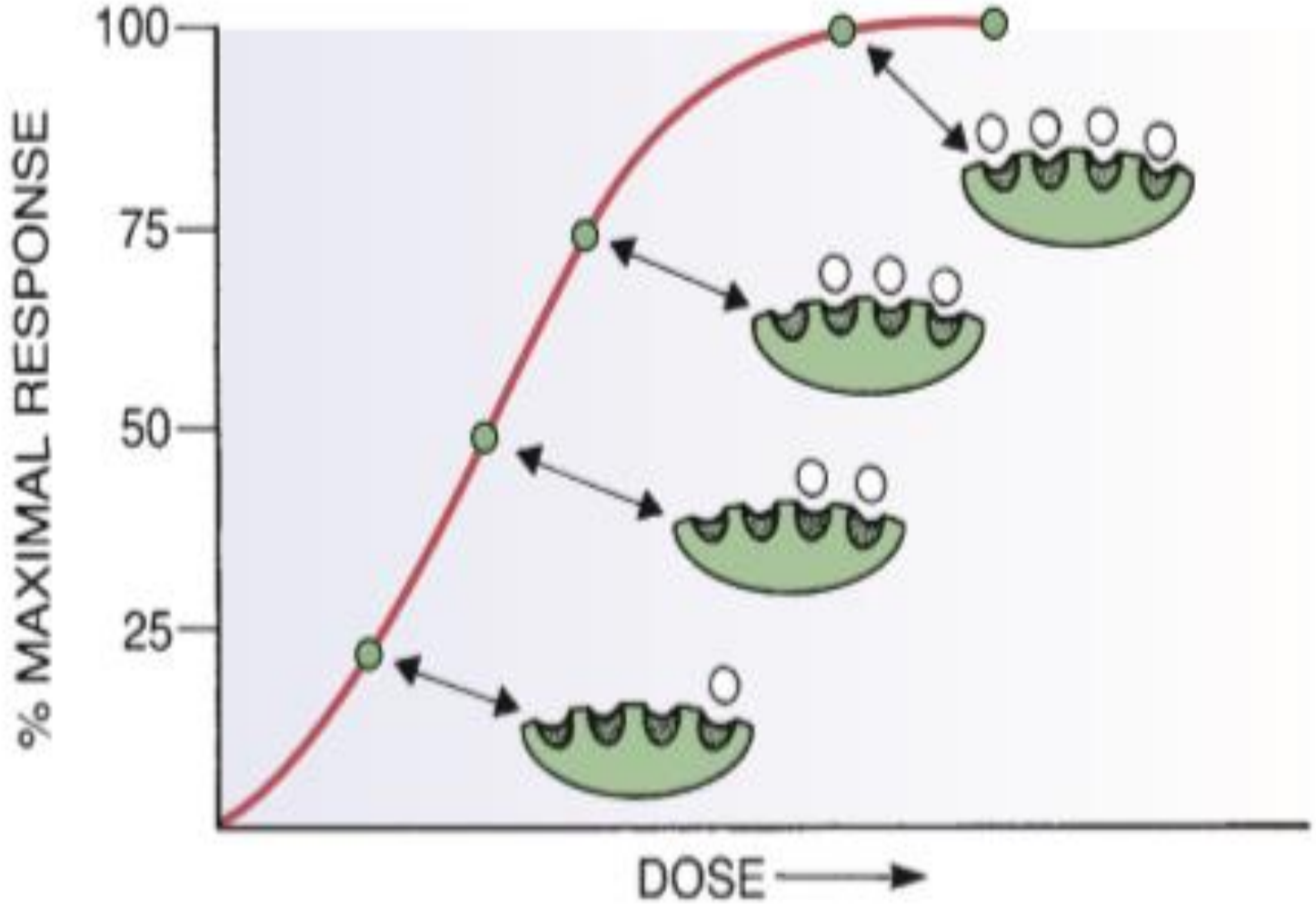


- **Receptors and selectivity of drug action**

- Selectivity is a highly desirable characteristic of a drug, in that the more selective a drug is, the fewer side effects it will produce.
- **Selective drug:**
- **Nonselective drug:**
- **Theories of Drug-Receptor Interaction**

1) The simple occupancy theory and
2) The modified occupancy theory.

- These theories help explain dose-response relationships and the ability of drugs to mimic or block the actions of endogenous regulatory molecules.



- The simple occupancy theory states that the intensity of response to a drug is proportional to the number of receptors occupied; maximal response is reached with 100% receptor occupancy.

- The modified theory ascribes two qualities to drugs: affinity and intrinsic activity.
- **Affinity:**
- **Intrinsic activity:**
- 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:**
- 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:
  - **Affinity:**
  - **High intrinsic activity**

- **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:**

- Antagonists have:
- **Affinity**
- **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) **Non competitive antagonists:**
2) **competitive antagonists:**

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.

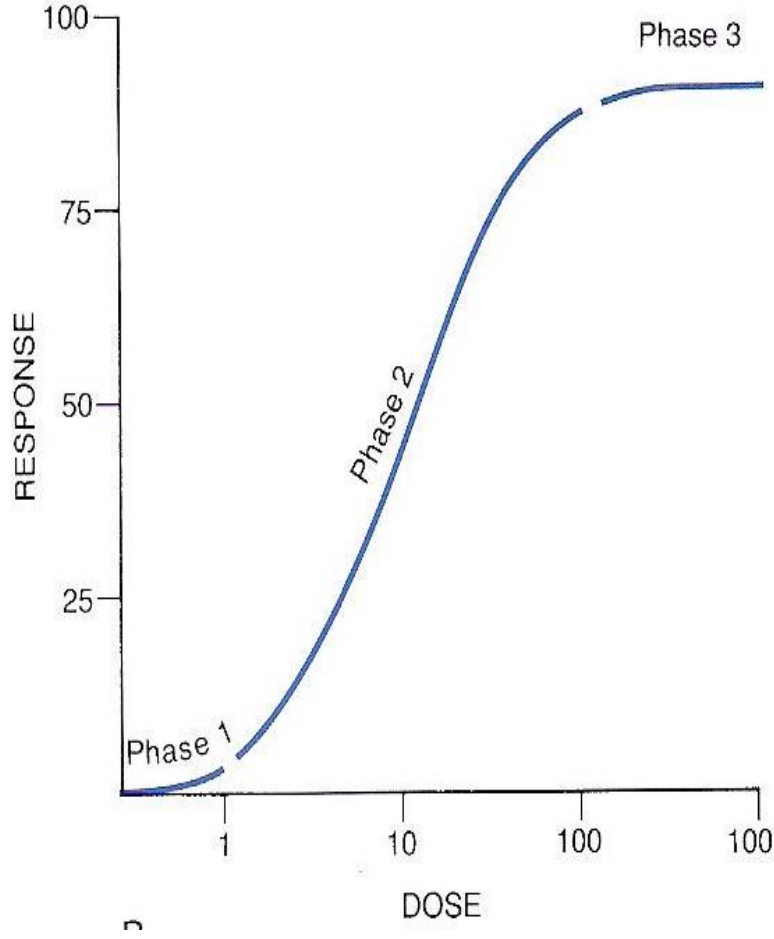
1. Desensitization or receptor down-regulation:

- 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

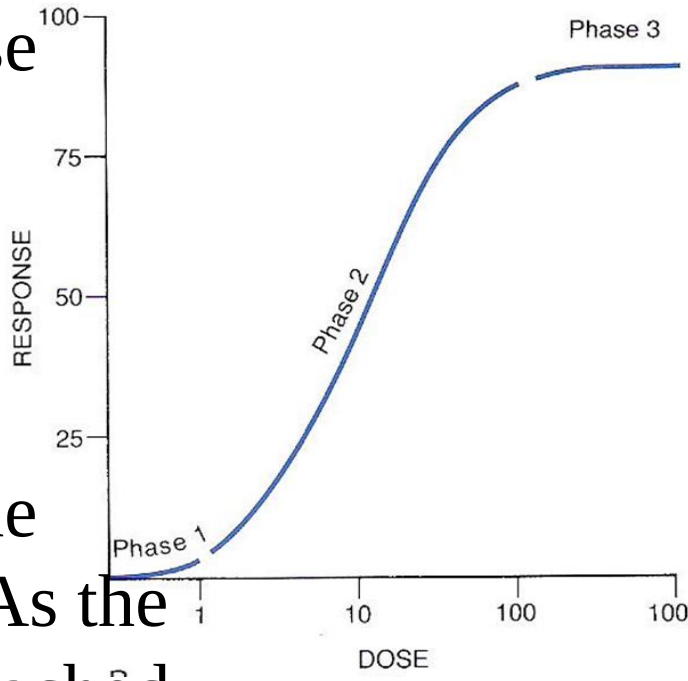
Dose–Response curve

- 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



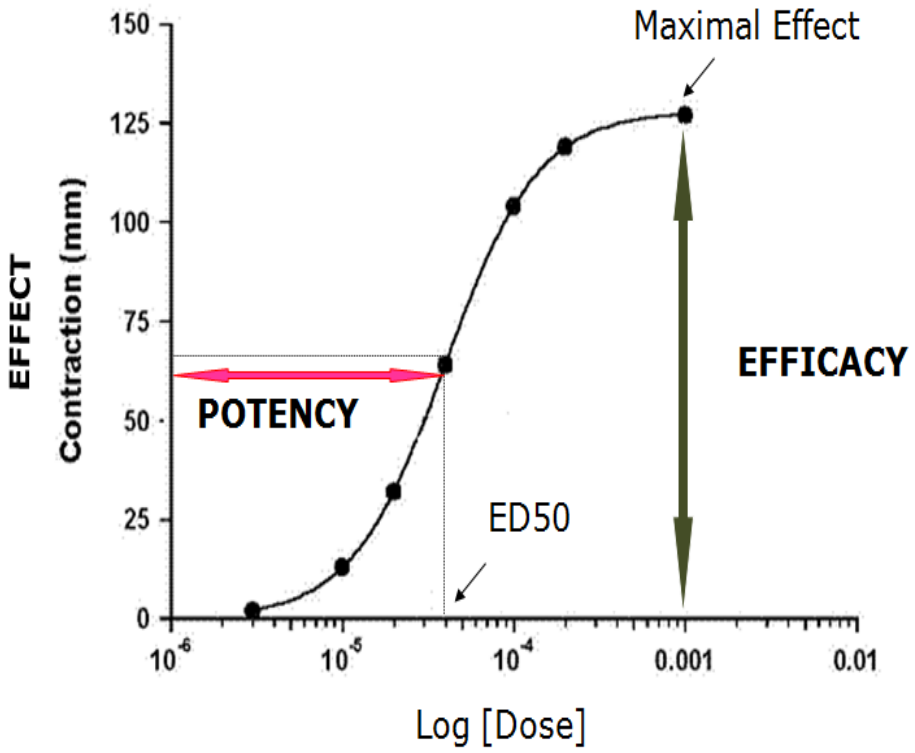
- The most obvious and important characteristic revealed by these curves is that the dose-response relationship is graded.
- The graded nature of the dose-response relationship is essential for successful drug therapy. That is, as the dosage increases, the response becomes progressively larger.
- Because drug responses are graded, therapeutic effects can be adjusted to fit the needs of each patient. ⇒ 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 ↑ in dose is unable to elicit a further ↑ in response. At this point, the curve flattens into ***phase 3***.

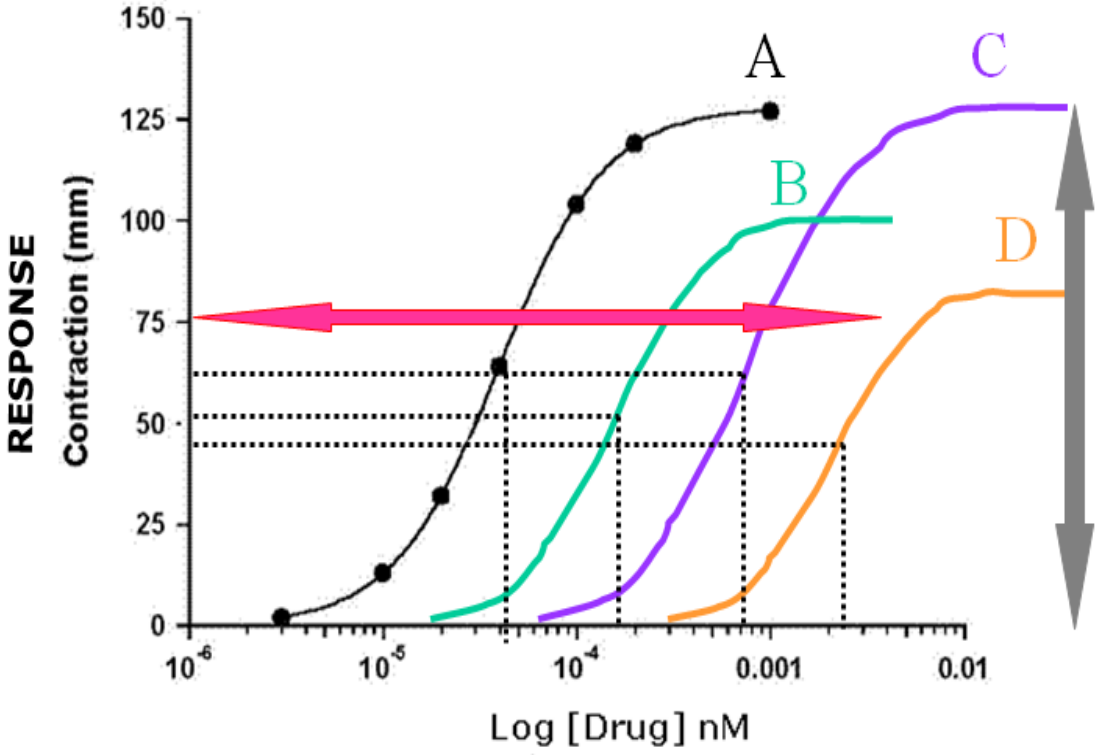


- Dose-response curves reveal two characteristic properties of drugs:

1. **Maximal Efficacy**
2. **Relative Potency**



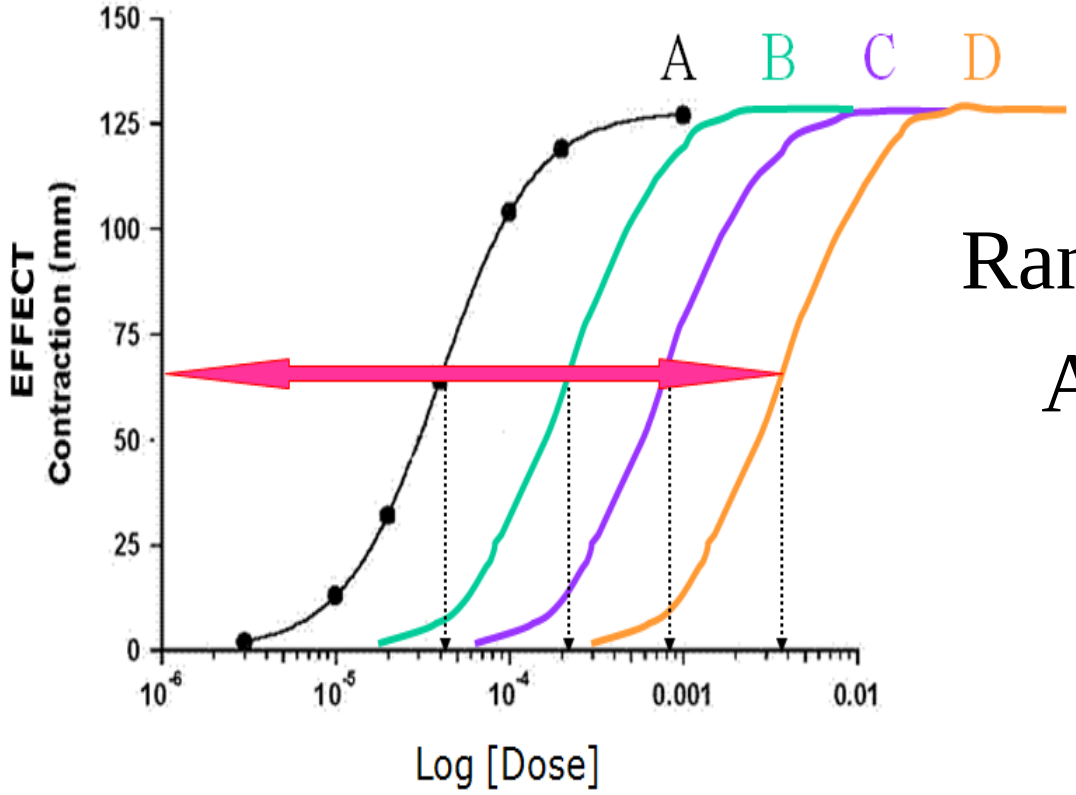
- E.g. if Drug A causes a greater maximum intensity of response than Drug B (regardless of dose), ➔➔ Drug A is more efficacious than Drug B



Rank order of efficacy:

A = C > B > D

A potent drug is one that produces its effects at low doses.



Rank order of potency:

A > B > C > D

Therapeutic Index and Drug Safety

Therapeutic index (TI): is a value representing a drug's safety or drug's margin of safety = the relationship between a drug's desired therapeutic effects and its adverse effects and determined by the degree between: Therapeutic dose and toxic dose.

TI was frequently determined in animals as lethal dose of a drug for 50% of the population (LD_{50}) divided by the minimum effective dose for 50% of the population (ED_{50})

$$\text{Therapeutic index} = \frac{\text{median lethal dose } LD_{50}}{\text{median effective dose } ED_{50}}$$

LD_{50} (Lethal dose that kills 50 % of animals tested)

ED_{50} (is the amount of drug that produces a therapeutic response in 50%)

$$\textbf{For human Therapeutic index} = \frac{\text{median toxic dose } TD_{50}}{\text{median effective dose } ED_{50}}$$

TD_{50} (Toxic dose – dose that will produce toxicity in 50% of a group of patients tested).

- Margin of safety → serum drug concentration within therapeutic range

  Meds with high TI= wide safety margin

  Meds with low TI= narrow safety margin

✸✸Drugs with a narrow or low therapeutic index have a narrow margin of safety – potentially danger. This means that there is a narrow range of safety between an effective dose and a toxic one. On the other hand, a drug with a high therapeutic index has a wide margin of safety – safe drug – and poses less risk of toxic effects.

- **The larger the TI, the safer a drug**
- E.g., Penicillin has a large TI, therefore therapeutic monitoring is not needed, whereas warfarin or digoxin that has a low or small TI and must have accurate therapeutic monitoring.

Adverse drug Reactions

- The drugs that produce useful, desired, therapeutic effect may also produce unwanted, undesired, harmful effect – **adverse drug reaction**.
- **Adverse drug reaction (**ADR), as defined by the WHO, is any noxious, unintended, and undesired effect that occurs at normal drug doses – excludes undesired effect that occur when dosage is excessive "toxicity". Adverse reactions can range in intensity from mildly annoying to life threatening.
- **Toxicity:** a harmful drug reaction caused by "excessive dosing" after prolonged intake of high doses of medication or after only one large dose because of accidental poison or medication errors.
- ADRs can occur with all medications – whenever a drug taken, a risk is taken. Fortunately, when drugs used properly, many ADRs can be avoided, or at least kept to a minimum

- Predisposing factors for adverse drug reactions

(High-risk groups)

- Age – adverse effects are more common in very old & the very young (Pts over 60 account for nearly 50% of all cases of adverse effects)
- Gender – increase adverse effects incidence in women
- Severe illness and multiple disease states
- Pts receiving multiple drugs than in pts taking just one

Types of adverse drug effects

Type A	**A**ugmented pharmacological actions	Can occur in all patient Largely predictable Usually dose-related They are common and skilled management reduces their incidence, e.g. postural hypotension, hypoglycemia, hypokalemia
Type B	**B**izarre reactions	Occur only in some people They are not part of the normal pharmacology of the drug, Not dose-related Due to unusual attributes of the patient interacting with the drug. Unpredictable for the individual The class includes unwanted effects due to inherited abnormalities (idiosyncrasy) and immunological processes
Type C	**C**hronic reactions	Due to long-term exposure, e.g. analgesic nephropathy
Type D	**D**elayed effects	Following prolonged exposure, e.g. carcinogenesis or short-term exposure at a critical time, e.g. teratogenesis.
Type E	**E**nding of use reactions	Where discontinuation of chronic therapy is too abrupt, e.g. of adrenal steroid causing rebound adrenocortical insufficiency, of opioid causing the withdrawal syndrome

General Adverse drug reactions

- **Allergic reaction:** (also called a **hypersensitivity** reaction)
- **Drug idiosyncrasy**
- **Drug Dependence:** Physical and Psychological dependency:
- **Drug tolerance:**
- **Cumulative drug effect**:
- **Iatrogenic disease**
- **A pharmacogenetic disorder:**
- **Gastrointestinal Effects**:
- **Organ-Specific Toxicity**
  - Hepatic effects
  - Nephrotoxicity
  - Hematologic effects
- **Carcinogenic effect:**
- **Teratogenic effect:**

- **Drug Interactions:** **Drug – drug interactions.**
- Drug-drug interactions can occur whenever a patient takes two or more drugs and the action of one drug interacts or interferes with the action of another drug.
- Drug interactions may occur when two or more drugs are administered at the same time or when a short time interval exists between the administration of two different drugs
- Some times patient need to take two or more drugs to treat a single disorder or to treat multiple disorders.
- They may take over-the- counter drugs in addition to prescription medicines.
- And they may take caffeine, nicotine, alcohol, and other drugs that have nothing to do with illness.
- Some interactions are both intended & desired e.g. combine drugs to treat hypertension.
- In contrast, some interactions are both unintended & undesired e.g. taking an antacid with oral tetracycline causes a decrease in the effectiveness of the tetracycline

- **Drugs can interact by way of four basic mechanisms:**

❶ **Direct chemical or physical interaction:**

– This interaction occur most commonly when drugs are combined in IV solutions. Frequently, but not always, the interaction produces a precipitate. If a precipitate appears when drugs are mixed together, that solution should be discarded. Because drugs can interact in solution, never combine two or more drugs in the same container unless it has been established that a direct interaction will not occur.

❷ **Pharmacokinetic interaction**

– Drug interactions can result in increased or decreased drug absorption, distribution, metabolism and renal excretion

❸ **Pharmacodynamic interaction**: Drugs that act as antagonists at a particular receptor will diminish the effects of drugs that act as agonists at that receptor →prevents toxic effects or prevents therapeutic effects of the agonist

❹ **Combined toxicity**. If drug A and drug B are both toxic to the same organ, then taking them together will cause more injury than if they were not combined.

Consequences of drug-drug interactions:

1. **Intensification of Effects -** Synergism interaction
2. **Reduction of Effects –** inhibitory interactions

Drug-food interactions

- Drug-food interactions are very important because they can result in toxicity and therapeutic failure.
- They are poorly understood because research has been sorely lacking.
- **Impact of Food on Drug Absorption**:
- **Impact of Food on Drug Metabolism:**
- **Impact of food on drug toxicity**
- **Impact of food on drug action**
-

Thank You