Introduction

Edition by
Dr.Firas Alaasam
M.Sc Pharmacology & Toxicology

L N (3)

Definitions:

1-Pharmacology: science dealing with → interactions between chemicals (drugs) and living systems.

2. Drug: chemical substances, when introduced into the body, alters the body's function, producing → biological effects . Can be:

- Stimulatory. * Inhibitory.

3. Prodrug: chemical, is readily absorbed and distributed and then converted to → active drug by → biologic process inside the body.

4. Toxicology: deals with the → undesirable effects of chemicals in biological system.

5. Pharmacogenomics (pharmacogenetics): study the → genetic variations that cause individual differences in drug response. Aren't found in general population (allergies), but due to→ an inherited trait that produces a diminished or enhanced response to a drug.

General concept of Pharmacology:

1. Pharmacodynamics: what the drug does to the body.

2-Pharmacokinetics: what the body does to the drug.

- Absorption.
- Distribution.
- Metabolism.
- Elimination.

2.Pharmacodynamic Phase

(What does the drug to the body)

Definition : it is the study of biochemical and physiological effects of drugs and their mechanism of action

Pharmacodynamics includes :

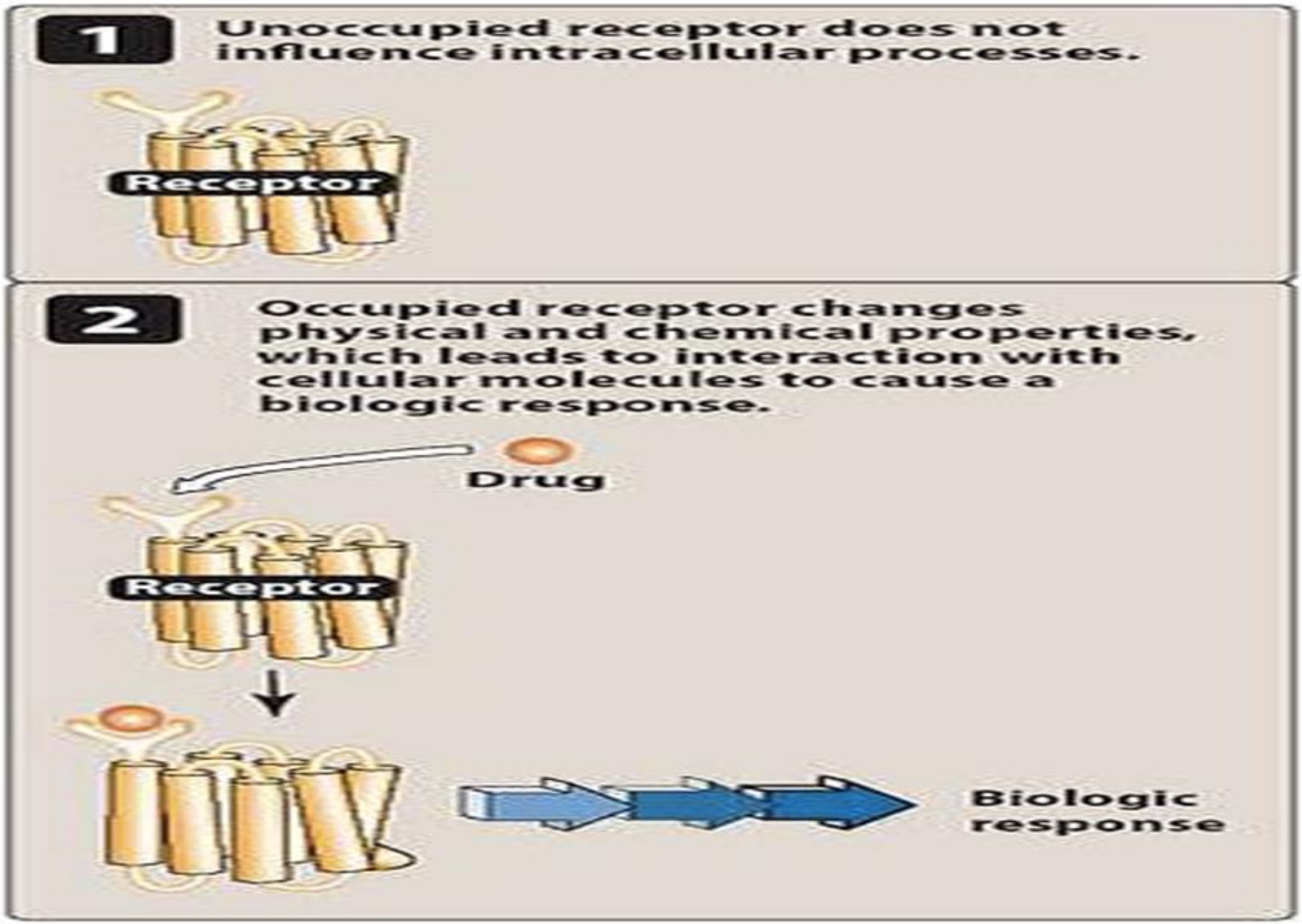
- **Mechanism of drug action**
- **Pharmacological effects**
- ***Body control system***

1-Action on specific receptors (drug receptor interaction):

 Receptors: are macromolecular protein structures, present on → cell membrane / within the cell.

2.Pharmacodynamic Phase

(What does the drug to the body)



2-Action on enzyme stimulation/inhibition:

enzyme inhibition could be:

- **Reversible:** short-term (Neostigmine → Cholin-esterase inhibitor).
- **Irreversible:** long-term for new enzyme synthesis (irreversible Anti-cholin-esterase).

3. Carrier molecule :

4. Interfere with selective passage of ions (Ca+2 and Na+ entry → local anesthetics drugs)

5. Interference with normal metabolic pathway (Sulphon-amides competes with PABA → essential for bacterial growth).

6-Physical action: alter the environment of the cell through physical action (Kaolin adsorbs toxins in → diarrhea).

7- Chemical action: alter the environment of the cell through chemical action ($NaHCO_3$ in → hyperacidity).

-*Therapeutic neutralization of gastric acid by base :* -

Eg: Antiacid

Receptor :

are the protein molecules in biological system with which drug **(Ligand),**hormone, neurotransmitter interact to produce change in the function of the system

Agonist:

It is a drug that binds to the receptor and produces a biological response

Antagonist:

It is a drug that binds to the receptor but no biological response is produced

Affinity:

It is the tendency of a drug to associate with its receptor. It is a measure of how tightly a drug binds to a receptor(Fast/strong binding = higher affinity)

--Types of Receptor

-Ligand –gate ion channel receptors

Ach + nicotinic receptors → Na+ influx → depolarization

These responses takes → milliseconds.

- G-protein coupled receptors

Eg : Serotonin , Muscarinic , Dopaminergic, Adrenergic

Second messenger → include:

1. cAMP (cyclic Adenosine Mono-Phosphate).
2. Ca +2 ion.
3. Phospho-ino-sitides.
4. cGMP (cyclic Guanosine Mono-Phosphate).

- Tyrosinase kinase linked receptors

Eg : Insulin,

4. DNA-linked receptors (intracellular receptor):

Eg: sex hormone, estrogen .cortisone

- When agonist bind to → the domain, hsp90 domain is → released

leaving the DNA binding domain, which regulates:

1. Gene transcription.
2. Translation.
3. Protein synthesis.

- Has a slow onset → long duration.

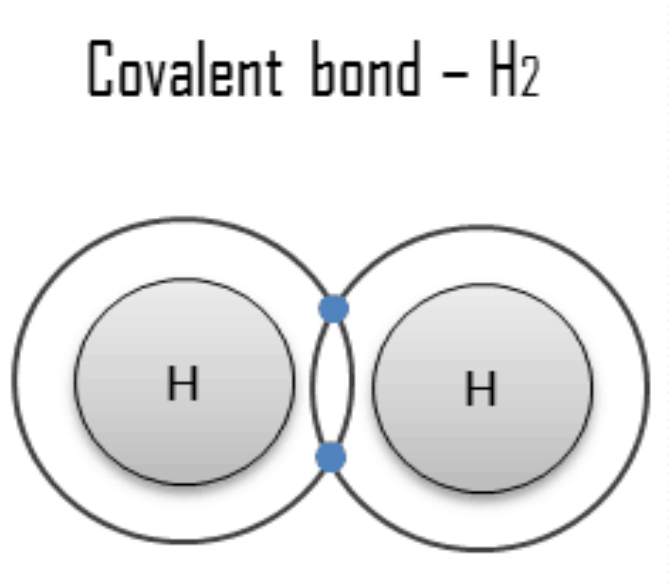
.

TYPE OF BOUND

1- H – pound its strong and reversible (H……H , H……O , H……..N)

2- ionic bound its strong and reversible .(+ ……. -)

3- covalent bound its very strong and take long duration of action and very strong and irreversible



Dose-Response Relationship

- When a Drug administered systemically
  - Dose-plasma concentration relationship (determined by pharmacokinetic properties)
  - Plasma concentration (dose)-response relationship
- Intensity of response increases with increase in dose / concentration at the receptor
- Drug-receptor interaction obeys law of mass action

Dose-Effect Endpoints

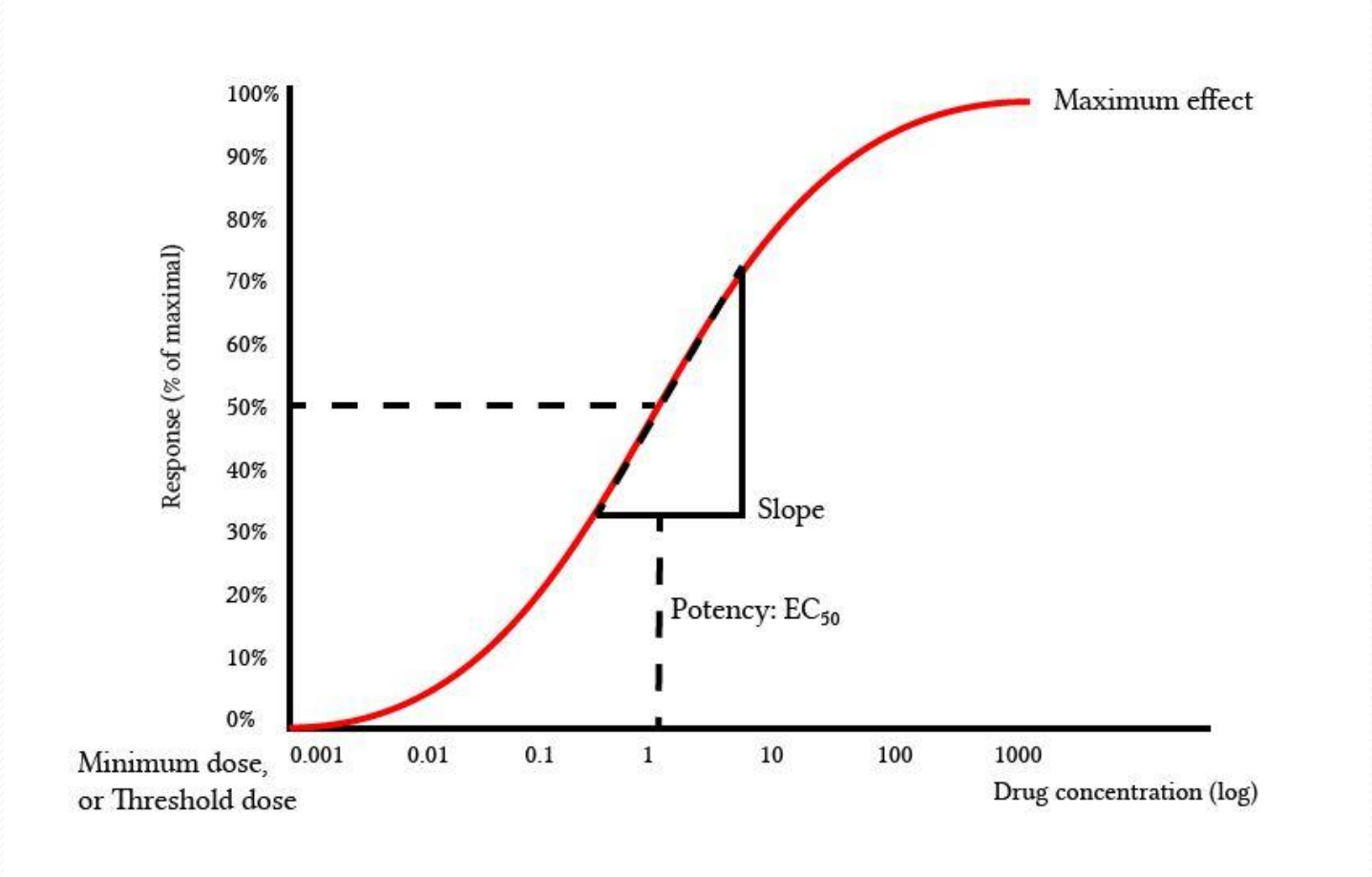
Graded

- Continuous scale (dose → effect)
- Measured in a single biologic unit
- Relates dose to intensity of effect

Quantal

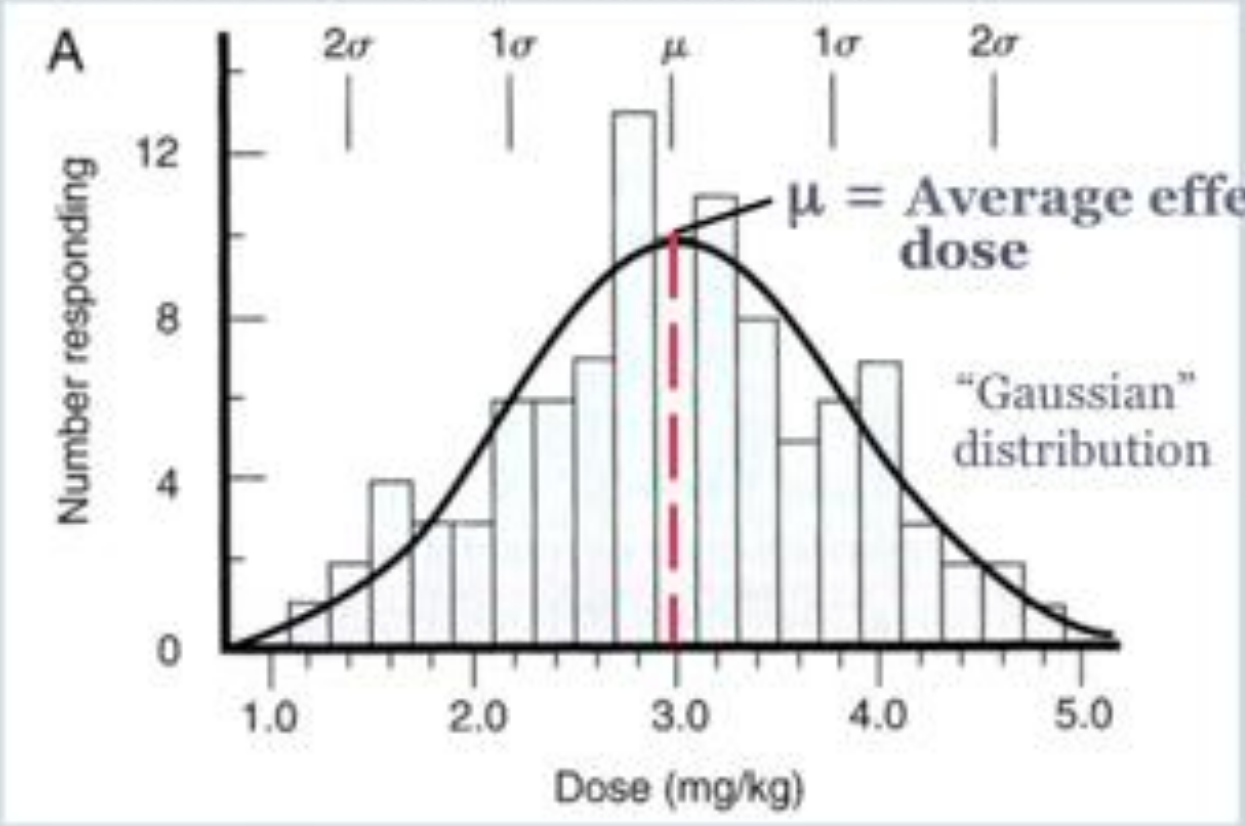
- All-or-none pharmacologic effect
- Population studies
- Relates dose to frequency of effect

GRADED RESPONSE



QUANTAL DOSE RESPONSE

Frequency distribution curve of drug doses



Determine the minimum drug dose required to produce a specified effect for each member of the population

Efficacy

It is the maximal response produced by the drug. It depends on the number of drug-receptor complexes formed.

ED50 "effective dose 50":

The dose of the drug that produces a response equal to 50 % of the maximum response.

Potency

It is a measure of how much of a drug is required to elicit a given response. The lower the dose required for a given response, the more potent the drug

LD_{50} is the amount of a material, given all at once, which causes the death of 50% (one half) of a group of test animals

Therapeutic index

It is the ratio of LD50 (the dose which is lethal to 50% of experimental animals) to ED50 (the dose that gives the desired response in 50% of experimental animals).

= LD50 / ED50

Therapeutic index is a measure of drug safety, thus the higher the index the safer is the drug.

Drugs can be categorized into:

Agonists	**Drugs which → stimulate receptors: initiate changes in cell function producing effects. Potency depends on: 1. Affinity. 2. Efficacy.**	**Affinity: tendency to bind receptors.**	**Efficacy: ability to initiate changes, which lead →effect.**	**Rapid Dissociation rate.**
Antagonists	Drugs which → block receptors; they bind to receptors without Produce any effect Have no effect in the absence of agonist. Prevent the action of agonists. .	Affinity.	No efficacy.	Slow dissociation rate.

Drugs can be categorized into:

Partial agonists	Stimulate and block receptors. .	Affinity.	Efficacy.	Moderate dissociation rate..
Full agonist				

Types of antagonists:

1-Pharmacological Antagonists:

A. Competitive	B. Non-Competitive
Compete for the binding site.	Bind anywhere in the receptor.
Reversible	Irreversible.
Surmountable.	Un-surmountable.
The effect can be overcome by more agonist (drug). Higher the conc. of antagonis used → more drug you need to get the same effect.	The effect cannot be overcome by more agonist (drug).
	Inactivates the receptors

Reversible

- The effect of reversible antagonist can be overcome by more drug (agonist)

- Higher the concentration of antagonist used, the more drug (agonist) you need to get same effect.

Irreversible

-Bind to the receptor with strong covalent bonds, irreversibly blocks receptors .

- The effect of a irreversible antagonist cannot be overcome by more drug (agonist)

2. Functional Antagonists:

2. Functional Antagonists:

1. Physiologic antagonist:

 Tow drug acts on different receptors, producing an opposite effect to that produced by the drug of interest

 Intrinsic activity = 1. but on another receptor

* Glucocorticoid hormones → ↑ blood sugar.

* Insulin → ↓ blood sugar.

2. Chemical and physical antagonist:

 Two drugs react together and form an inactive product .

- eg: Heparin (acid,) and protamine sulfate (base)
- Reason : protamine forms a stable inactive complex with heparin and inactivates it .
- **4- pharmacokinetic antagonist**
- Absorption , distribution ,metabolism , elimination

Factors modifying drug response

variations in response to same dose of a drug between different patients • in the same patient on different occasions

1-BODY WEIGHT : average dose of a drug is mentioned in terms of mg/Kg body weight. However, the dose mentioned may not be applicable to all cases. • in cases of edema weight of patient increases due to the accumulation of ECF in malnutrition metabolizing capacity of drug is reduced these factors should be kept in mind while calculating the dose of drug

2-Age : Pharmacokinetics of many drugs change with age. - Newborn: liver and renal function less developed – Elderly: hepatic and renal functions decline – Glomerular filtration rate: low in infants – Blood brain barrier: more permeable in infants & may cause accumulation

Factors modifying drug response

3 SEX: • Females: smaller body size, require doses that are on lower side of the range. • Consideration given to menstruation, pregnancy and lactation. • Drugs given during pregnancy may affect the fetus. • Physiological changes during pregnancy alter drug disposition. • drugs like methyldopa and □ blockers interfere with sexual function in males but not in females.

4-GENETIC FACTORS: • The dose of a drug to produce same effects may vary 4–6 folds among different individuals. This is mainly due to the differing rates of drug metabolism as the amount of microsomal enzymes is genetically controlled. • There are some specific genetic defects that lead to variation in drug response. Example; • Hemolysis by Primaquine and Sulfonamides in persons with G.6.P.D. deficiency. • Slow metabolism of Isoniazid in slow acetylators.

Factors modifying drug response

5-TIME OF ADMINISTRATION: There is delayed drug absorption when drug is given orally after meals, which slows down the effects of drug. Under certain circumstances drugs must be given before meals. • To prevent mixing of drug with food Anthelminthics. • To get immediate effect: Drugs used for prevention of motion sickness. • To prevent formation of insoluble complexes: Tetracycline's. • To prevent specific side effects, for example to prevent hypoglycemia insulin and sulfonylureas are given before meals

6-METABOLIC DISTURBANCES: Changes in water and electrolyte balance body temperature and acid base balance may modify the effects of drug. • For example aspirin reduces body temperature only in presence of fever and have no effect on body temperature when it is normal. • Iron is well absorbed in states of iron deficiency.

7-PATHOLOGICAL CONDITIONS several diseases influence drug disposition and action. • Hepatic, renal and cardiovascular diseases have important influence on drug clearance and drug actions. • Drugs must be carefully used in presence of diseases of these organs

Factors modifying drug response

8-Drug interaction: • Drugs may modify the response to each other by pharmacokinetic or pharmacodynamics interaction between them. • Drug interaction does not necessarily mean that their concurrent use is contraindicated; many drugs can be used beneficially and some with dose adjustment. • Drug combinations can produce

ADDITIVE EFFECT OR SUMMATION When total pharmacological effect produced by concomitant use of two or more drugs is equal to the sum of their individual effects, it is called "Additive effect." 1 + 1 = 2

SYNERGISM • When total pharmacological effect produced by concomitant use of two or more drugs is higher than the sum of their individual effects, it is called

"Synergism". • 1 + 1 = >

Factors modifying drug response

POTENTIATION • Enhancement of effect of one agent by another; so that the combined effect is more than the sum of their individual effects is called “Potentiation.” • In case of potentiation one agent has no effect when given alone but increases the effects of other co-administered drug. • 0 + 1 = > 2. • Example: • Levodopa + Carbidopa => Parkinsonism. • Ampicillin + Clavulanic acid = > Antibacterial effect.

ANTAGONISM •


Thank you