Pharmacology :

Wide term which includes:
- The investigation of the **biochemical and physiological effects** of drugs
- The study of drug **absorption; distribution; metabolism and excretion**
- The knowledge about the **history; sources; physical and chemical properties and therapeutic uses** of drugs

Drug :

A chemical substance that is primarily used to reverse a pathophysiological defect = disease
= **all chemicals may be drugs**
= **All drugs are toxins but not all toxins are drugs**
* FDA approved definition of drugs :
A chemical substance that is mainly used to treat, control, prevent, or diagnose a specific disease or to prevent pregnancy!!!

Chemical nature of drugs

- **Acidic**; Aspirin, barbiturates...etc
- **Basic or alkaline**; Morphine, Atropine, Alkaloids...etc
- **Neutral**; Steroids

MAJOR OBJECTIVE
TO HAVE DRUG AT SITE OF ACTION IN PROPER CONCENTRATION GOOD ENOUGH TO REVERSE DEFECT WITHOUT PRODUCING SIDE OR TOXIC EFFECTS

- **Pharmaceutical process; drug in dosage form:**

Is the drug getting into patient?

- **Pharmacokinetic process:**

Is the drug getting to its site of action?

- **Pharmacodynamic process:**

Is the drug producing the required pharmacological effect?

• Therapeutic process (clinical pharmacology):
Is the pharmacological effect being translated into therapeutic effect?
• Phrmacogenetics
Individual variations in responding to drugs + gene therapy

Drug discovery & development

1. Starts with **prediction** = an idea & hypothesis What helps?
- **Awareness** of the beneficial effects of plants and animal products (natural sources)
- **Chemical identification** of a wide variety of natural mediators and the possibility of modifying them chemically e.g. *epinephrine, norepinephrine, acetylcholine, histamine, prostaglandins, endogenous opioids, hormones...etc*
- **Avoid** chemicals with highly reactive groups (**toxic**)

2. **Design** and **synthesis** of useful drugs or substances through simple techniques or with the help of advanced technology
e.g.
plant → fractionation, chromatographic experiments → identification of the active ingredients → isolation → purification →
good drug (recently most drugs of plant source could be synthesized)

Animal → isolation of a substance (Thyroid hormones; insulin...)
Human → isolation of a substance (HMG's) Simple peptides → a.a sequencing machine Complex proteins → recombinant DNA technology=genetic engineering
- Receptology studies allowed synthesis of huge number of agonists and antagonists

3. **Preclinical studies :** Studies on tissues and whole animals
- **Determine efficacy** by Isolated tissue e.g. bronchi → organ path → testing drug...etcAnimal models
→ drug ↓ BP
→ drug ↓ blood sugar level

- **Determine pharmacokinetic parameters :** Absorption, distribution, metabolism...etc
- **Determine pharmacodynamics (MOA)**
- **Assessment of drug toxicity=safety** :

Acute toxicity studies determination of LD50; margin of safety...etc
Subacute and chronic toxicity studies Repeated dose studies

This by Daily observation of animals (wt., food and water intake ..)
And Obtaining biological samples (blood; urine)
Also Obtaining tissues (liver; spleen; stomach ...etc) for histopathological exam or studi

Special toxicology studies
.**Mutagenicity (genotoxicity**) tests Could delineate the induction of gene mutations (bacterial mutagenicity test or administration of drug to pregnant animals...etc).
Some mutations could result in the development of cancer
. **Carcinogenicity studies** Not always required prior to early studies in man unless there is a high suspicion that the drug could be carcinogenic e.g. suspicion of mutagenicity; highly reactive groups on drug; histopathological abnormalities...etc) Required if the use of drug in man for more than one year or + ve mutagenic test

Clinical drug trials (mainly 4 phases)

- Phase 0

or first-in-human trials is a recent phase approved in accordance with the US FDA It's also known as human microdosing studies and are designed to speed up the development of promising drugs by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies

Distinctive features include: the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics and

pharmacodynamics
A Phase 0 study **gives no data on safety or efficacy,** being by definition a **dose too low** to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development

Phase 0 studies enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data Questions have been raised by experts about whether Phase 0 trials are useful, ethically acceptable, feasible, speed up the drug development process or save money, and whether there is room for improvement

- Phase I

Involves the **use of a drug in humans for the first time** (safety)
It establishes dose level at which signs of toxicity first appear
Conducted on 20-80 **healthy** men with ages 18-45 y

Usually a single dose is used initially and if no side effects exhibited, the **dose is increased progressively** until sufficient serum level is achieved **(therapeutic level)** or some toxic effects appear.
Such studies are conducted in hospital
If no side effects result from single dose, multiple dose studies should be initiated=bioavailability-bioequivalence studies

- Phase II

the new drug is administered **to patients** for the first time
All patients should have **only one problem** (one disease)
It assesses **efficacy & safety** and establishes optimal dose range in patients (dose-response studies are important)
conducted on 80-100 patients (certain countries ask for 50-300 patients)

- Phase III

Similar to phase II but conducted on large number of patients (several hundreds to thousands; 250-1000 reasonable)
It also assesses safety and efficacy
Could detect effects/side effects not observed in phase II

- Phase IV

Post-marketing studies
Controlled and uncontrolled studies are often conducted after drug approval and marketing
It further assesses safety & efficacy of drugs
It allows for comparisons between different drugs used for the same disease
Could provide **evidence of a new use to the drug** e.g. aspirin-antiplatelet sildenafil citrate-ED
Double-blind; single-blind placebo controlled studies are usually conducted

AFTER ALL THESE CLINICAL DRUG TRIALS THE DRUG IS USUALLY APPROVED BY NATIONAL ORINTERNATIONAL REGULATORY AUTHORITIES AND IS LICENSED FOR GENERAL PRESCRIBING

Ethics of the use of drugs in humans

- Full detailed protocol has to be approved by the ethical committee, the institutional review board (IRB)
- All subjects should **sign** an informed consent form
- All subjects should be **insured** for life and damag

Topical = local administration

- Liquid forms (sprays, lotions, solutions = ear or ophthalmic drops, mouth washes, S.C infiltration e.g. local anesthetics...)
- Semisolid forms (creams, ointments...)
- Solid forms (suppositories, pessaries = vaginal tablet...)

Routes of Administration of drugs

- ENTERAL: Via gastrointestinal tract (**GIT**)

Nasogastric

Oral (Swallow) :

Dosage form:

Tablet, Capsule, Powder, Solution, and Suspension

Advantages:

Convenient (to most patients), self medication, cheap, relatively safe, large volume may be given, does not require maximal sterility

Disadvantages:

Absorption is unpredictable, slow onset of action, impossible to use in unconscious or in vomiting patients, some drugs may be destroyed by gastric acidity, presence of food or other drugs may interfere with absorption. Undergoes first-pass metabolism

Rectal:

Dosage forms:

Ointment, solution, suppository and Jelly

Advantages:

Avoids gastric irritation, may be used in unconscious patients or vomiting patients or who are unable to swallow. Useful in children. Avoids first-pass metabolism

Disadvantages:

Inconvenient to the patients (Discomfort), absorption is slow and incomplete, irritation and inflammation to rectal mucosa

Sublingual:

Dosage forms:

Tablet, solution and aerosol

Advantages:

Rapid onset of action, not destroyed by acidity, avoids firstpass metabolism

Disadvantages:

Not suitable for large volumes, poor absorption in vomiting patients, bitter or irritant and water-soluble drugs cannot be given

- Parenteral: Other than GIT (injection)

Intravenous:

Dosage forms:

Solution

Advantages:

100% bioavailability, no absorption is required, fastest onset of action, administration of large volume of drug, avoids first-pass metabolism

Disadvantages:

Often inconvenient, require maximal sterility, self medication is not possible, difficult to reverse acute adverse effects, increased risk of infections

Intraarterial, Intrathecal, Epidural, Intracardial, Intraperitoneal Intrapleural, Intraarticular, Intradermal, Subcutaneous, Intramuscular

- Topical / site specific

Transdermal:

Dosage forms:

Patch

Advantages:

Used for slow continuous administration, prolonged duration of action, no first-pass effect, minimal adverse effects

Disadvantages:

Only a small number of drugs can be used by this route, slow onset of action, could lead to local reactions

Inhalational (sprays), Epidermal, Conjunctival, Nasal, Vaginal,Urethra

Factors affecting the dose

Age, weight, sex, rout of administration

Factors affecting administration

- Physicochemical properties of drugs
- Site of action
- Status of patient
- Dosage interval

Drug sources:

- **Natural :** Plants (atropine, digoxin), animals (thyroid hormones; insulin), human (HMG's)
- **Semisynthetic** (many antibiotics)
- **Synthetic** (agonists; antagonists)

Drug nomenclature:

- **Chemical name** according to chemical structure e.g. acetyl salicylic acid
We don't use it
- **Generic name**; nonproprietary; official; approved name... Aspirin
It is the name that is given to a drug according to its active ingredient that makes it work
It is **the most** widely used in pharmacology
- **Trade name:** Proprietary; brand name Remine®; Bufferin®...etc

Pharmacokinetic process

It is the study of what the body does to a drug
It includes the processes:

1. Absorption

Passage of drug from **site** of administration to **circulation** and then distributes to reach its target organ (site of action)

Behavior of drugs in the plasma:

- **Bioavailability**:

The fraction of the given dose **that gets into blood (apply for oral)**
The bioavailability of an **I.V** given drug is **100%**
(low bioavailability = low effect)

- **Protein binding**, Represents:
A reservoir to the drug
A mean by which drug reaches its site of action
A major site of drug-drug interactions
(Strongly bound drugs to blood proteins remain longer in blood) , have longer t1/2 & DOA

The free form of the drug, is the form which is active and crosses membranes
(e.g. 50% of a given drug is albumin bound, means that 50% of the drug which is present in plasma is albumin bound)

- Sites of drug absorption:

Oral mucosa (buccal; sublingual tab.), **Stomach** (aspirin)
Intestine (major site; iron; vit. B12), **Lungs** (general anesthetics)
Rectum (suppositories), **Skin** (local preparations)

Factors affecting absorption:

Drug size (Most drugs have MW's between 100 and 1,000)
Lipid solubility (major factor)
Lipid/water partition coefficient
Degree of **ionization** or environmental **pH**:
Henderson-Hasselbalch Equation

$$pH = pKa + \log [A^-]/[HA]$$
$$pH = pKb + \log [BOH]/[B^+]$$

Ionization of drugs is the process by which **positively or negatively** charged ions are formed in a solution.
Most of the drugs are **organic** compounds (weak acids or weak bases).
The organic drugs are not completely ionized in the fluid, they exist in ionized and nonionized forms

Ionization of drugs **depends on the pka** of the drug **and the pH** of the medium.
The Ka for an acid or the Kb for a base of a molecule is a measure of its strength as an acid or base.
The pK of a drug is the pH at which the concentration of the ionized and nonionizedforms are equal (i.e. 50% ionized and 50% non-ionized)

Polar groups: O, NO2, COOH, OH...etc
(ionized; water soluble) form is the pharmacologically active form

Non polar groups: - S; halogens; Ch3
(unionized; lipid soluble) form crosses membranes

Cont. factors affecting absorption:
- Concentration of drug = dose
- Surface area of absorption (the larger the better)
- Blood circulation to absorbing area
- Route of administration (I.V the fastest)
- Dosage forms
- Food (1 hour before/after lunch)

2.Distribution

Passage of drugs from **blood** to different **tissues (site of action)**
Extent of distribution could be measured by a constant known as **AVD**

Apparent volume of distribution (AVD):
The **total volume** in which the free form of a given drug **distributes** in different body compartments **at equilibrium**

$$AVD = Dose\ (mg)/C0(mg/L)$$

C0 = Concentration of drug in blood at time zero

Highly lipid soluble drugs e.g. digoxin, have a very high Vd (500 liters).
Drugs which are **lipid insoluble** e.g. neuromuscular blockers, remain in the blood, and have a low Vd.
Very very high Vd indicates extensive tissue binding

Factors affecting drug distribution:
- Compartmental selectivity (IC or EC)
- Organ selectivity
- Protein binding (Major factor)
- Natural barriers : BBB, Placenta , Mammary glands

A High Vd

Indicates **significant distribution** or uptake by many tissues
A high Vd is commonly associated with **very long half-life to a given drug**

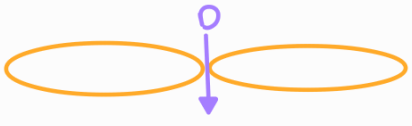
A low Vd

Usually denotes that **the drug is mainly in the plasma** i.e. high plasma concentration and low tissue distribution and binding

High or extensive plasma protein binding may result in:

- Restricted drug distribution
- Reduced intensity of pharmacological effects
- Predisposes the drug to many interactions
- Increases drug's duration of action (half-life)
- Decreases drug's AVD

Mechanisms of drug transfer across membranes:



Simple diffusion

Crossing **through water pores** of membranes, **no energy or carrier required, from high to low** concentration, drugs with low M.W (**must be lipid soluble** and concentration gradient is the driving force)

Passive diffusion (major mechanism)

Crossing **through cells or the lipid bilayer**, **no energy or carrier** required, **from high to low** concentration
The only requirement for passive diffusion is that the drug **should be lipid soluble**

Facilitated diffusion

Requires a carrier, no energy required, **from high to low** concentration

Active transport

Requires energy ± carrier, could be **from low to high** concentration
(Facilitated diffusion and active transport follow saturation kinetics because No. of carriers is limited)

Endocytosis
Phagocytosis (solid particles)
Pinocytosis (fluid particles)

3.Drug metabolism

A **change in the chemical structure** of the drug, or addition of a hydrophilic groups to an initially lipophilic drug until it becomes sufficiently ionic **so as to be easily filtered and excreted by the kidneys.**

The rate of metabolism (Km) of a given drug depends upon the chemical characteristics of the drug and has nothing to do with the benefit or harm of the drug

involves 2 major pathways:

Pathway I = **Oxidation reduction reactions**, Also known as mixed function oxidase system and cytochrome P450 system (CYPs=A;B...)

Examples:

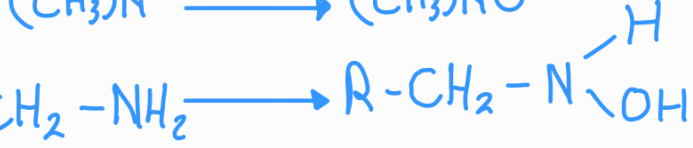
Aromatic hydroxylation

Aliphatic hydroxylation

O-dealkylation

N-dealkylation

N-oxidation; N-hydroxylation

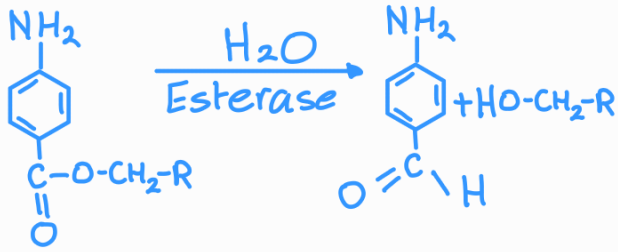


Sulfoxidation

Hepatic reduction
Azo reduction

Nitroreduction

Nonmicrosomal oxidation and reduction
Alcohol oxidation; chloral hydrate reduction
Hydrolysis reactions



Pathway II = **Conjugation reactions**
Addition of certain groups to a drug to **become more polar** and readily excreted

Acceptor + Donor —(soluble enzymes in cytosol of liver (transferases))→ conjugate
(Drug) (activated)

The addition:
Metylation, Acetylation, Glucuronic acid conjugate, Etheneal sulfates, Glycine conjugate (mercaptopuric acid formation)

Metabolism is all about to inactivate the drug by delivering it's metabolites to **kidneys**, then **excrete** them outside the body.

some of the drug go:
Inactive drug >>> active drug >>>> kidney
Inactive drug >>> active drug >>>> pathway I >>>> kidney
Inactive drug >>> active drug >>>> pathway 2 >>>> kidney
Inactive drug >>> active drug >>> pathway 1 >>> Pathway 2 >>> kidney
Inactive drug >>> active drug >>> pathway 2 >>> Pathway 1 >>> kidney

Characteristics of an ideal metabolite:
In order to be excreted
Water soluble, Pharmacologically inactive, Not to be toxic

Sites of drug metabolism:
Liver **(major site)**, Intestine, Lungs, brain, kidney, plasma, adrenals...etc

Factors affecting drug metabolism:
- Genetic factors and species differences **(major factor)** (slow and rapid metabolizers)

- Sex
- Drug-drug interactions
- Age (paracetamol vs chloramphenicol)
- General health of patients and nutritional status
- Dose and frequency of administration

First pass effect:
is the phenomenon which occurs whenever the drug is administered **orally**, enters the **liver**, and suffers extensive biotransformation (conjuncation- pathway2) to such an extent that the bioavailability is drastically reduced.
It happens when the drug is **absorbed through GIT** and then via the enterohepatic circulation the drug is absorbed directly into the liver where it undergoes metabolism before being released into the systemic circulation .

Inducers :
they **speed up the metabolism** thus reduce the activity of the drug.In such cases, higher doses are needed.
Ex: **Barbiturates, Theophylline, Phenytoin, Rifampicin, Allopurinol, Smoking** 🚬

Inhibitors:
lower the speed of metabolism thus increasing the activity of the drug. Here, lower doses are needed.
Ex : **Ketoconazole, Fluconazole, Cimetidine, Erythromycin, Contraceptives, Diltiazem, Grape fruit juice** 🍇

4. Drug excretion = elimination

A process by which a drug or it's metabolites are eliminated from the body
Its Major sites:
Kidney **(most drugs)**, or Liver if kidney has disfunction with kidney
if someone has disfunction with the both, we reduce the dose.

Methods of excretion:

- **Filtration**
- **Tubular secretion**

Specific secretory mechanism for weak acids and another one for weak bases **(80% of drugs are excreted by this mechanism).**
Still some drugs remain lipophylic so could be reabsorbed (this could be inhibited by changing pH and provides the use of alkali in enhancing excretion of acidic drugs)

Probenecid
Penicillin

The rate of excretion of a given drug is determined by a specific constant known as **Ke** which **depends on AVD and clearance**

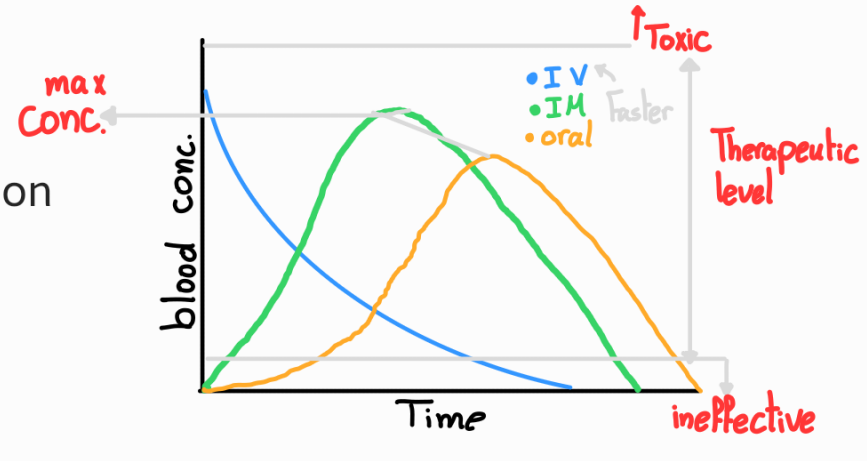
$$\text{Clearance} = \frac{Ux(mg/ml) \times V}{Px(mg/ml)}$$

Renal clearance is the volume of plasma cleared of drugs per unit time

Ke = Clearance (ml/min)/AVD (ml)
Ke unit: min-1 = 1/min
Ke = 0.693/t1/2(min)
t1/2 = o.693 × AVD/clearance
KT = Km+ Ke

the relationship between concentration of the drug in the blood and time(depending on the type of ADMINISNTRATION)

in oral administration: the drug's concentration will increase in the blood as a result of the absorption of the drug until all of its bioavailable dose is absorbed so it reaches itshighest concentration (the peak)

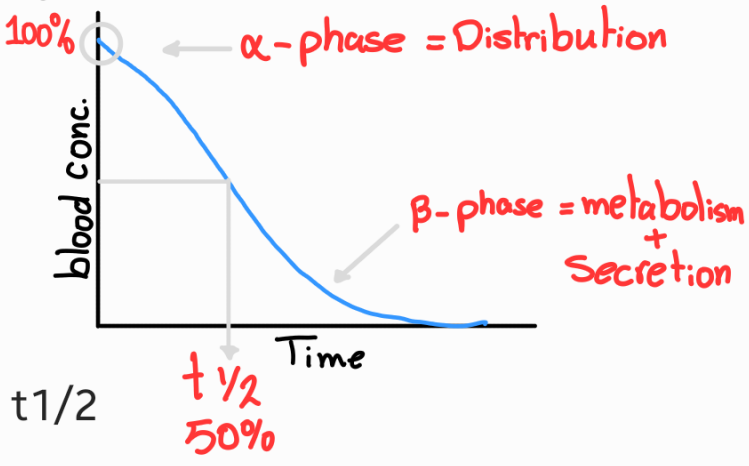


- The cause of the initial decrease (fall) of concentration is mainly due to distribution (which means the movement of the drug from the blood to the intended tissue)
- decrease in blood concentration is due to excretion

MAKE SURE THAT THE DRUG IS STILL IN THE THERAPEUTIC LEVEL)

- THE only one that reach its **highest concentration at time zero is (IV)**
(it does not need to be absorbed- all drug enter the circulation directly)

t1/2 life (the time it takes for the amount of a drug's active substance in your body to reduce by half
(decrease by 50%)
100 -> 50 -> 25 -> 12.5
t1/2 t1/2 t1/2



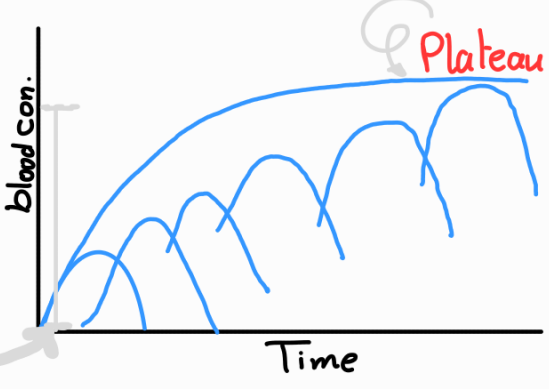
More lipid solubility = more AVD = high t1/2
More protein binding = t1/2 increases

Steady state level (chronic administration)

With chronic or repeated administration the amount of drug in the blood accumulates until it reaches the plateau
(steady state level = The amount of drug given = the amount that is eliminated)

STILL WITHIN THERAPEUTIC LEVEL

Reached after 5 t1/2 lives
Loading dose (initial large dose) followed by maintenance dose e.g. digitalization...etc



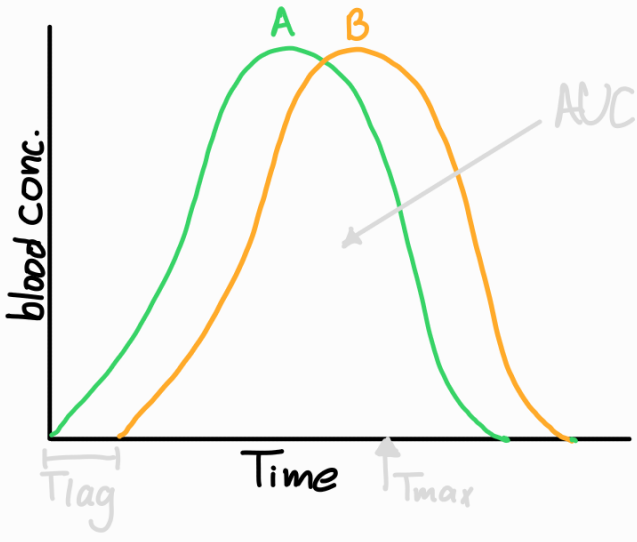
Trough and peak drug levels:

Used to establish the effectiveness of a drug Trough is the lowest drug level that is needed to reach therapeutic range.
Peak is drawing the serum blood levels (30 min parenteral; 1-2 hr oral) after the drug is administered.
Trough is drawing the serum blood levels right (30 min-1 hr) before the

next dose(If trough or peak levels are > than normal, the patient is at risk for adverse effects)

Bioavailability-bioequivalence studies:

To prove that **2** drugs have the **same**
Chemical structure, Bioavailability, Biochemical activity, Therapeutic effects



Terms and definitions

- Dose
It represents the amount of a drug to produce an effect

- Therapeutic dose
A dose which is required to produce a therapeutic effect

- Toxic dose
The dose which produces a toxic effect

- Half-life (t1/2)
It is the time by which plasma concentration of a drug falls or declines by 50% of its maximum concentration

- Steady state concentration
It is the concentration of a drug at which the rate of administration is equal to that of elimination of that drug. It usually takes 5 to 6 half-lives of a drug

- Loading dose
A large initial single or multiple doses are given for some drugs to achieve a rapid steady state concentration

- Maintenance dose
The dose which is used to maintain the steady state concentration or to maintain the therapeutic effect of a drug. It is given at a fixed interval time

- Tolerance
When repeated administration of an equal doses of a drug for a prolonged period of time (chronic administration) results in decreased responses.
Original responses can be obtained by increasing the dose (e.g. drugs of

addiction)

- Tachyphylaxis

Rapidly developing tolerance. When repeated administration of a drug produces decreased responses within a short period of time (even with 2 or 3 doses).

This phenomenon is usually observed in the laboratory

- Capacity limited processes

1. First-order (exponential) kinetics

All pharmacokinetic processes (abs., distr., met. excr.) occur at a rate directly proportional to conc. of drug e.g. increasing dose increases these processes

It represents that **the rate of elimination** of the drug from the body is **proportional to the concentration** of the drug in the plasma or blood

A percentage of the drug is eliminated per unit time.

Half-life of the drug is constant

irrespective of the doses used. Most of the drugs are eliminated by this process. **The curve is exponential**

First order kinetics may become zero order when high conc.'s of drug are present

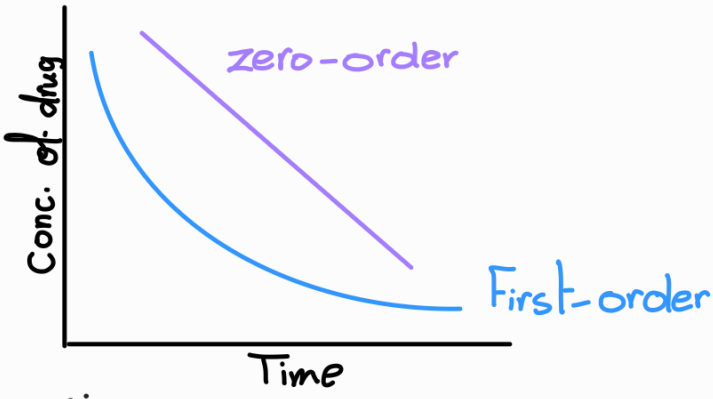
2. Zero-order (saturation) kinetics

Apply mainly to **met. and elimination** where their rates reach saturation (maximum) and a further increase in rates is impossible despite an increase in dose (these processes are independent of the conc. (absorption from SR tab. or continuous infusion are good examples)

The rate of elimination is **not proportional to the concentration** in the blood or plasma. A certain fixed amount of the drug is eliminated per unit time

This process is saturable and half-life may be increased if the dose of the drug is increased. A few drugs follow this process.

The curve is a straight line i.e. not exponential



- Indications

Clinical uses of drugs

- Contraindications

Situations when not to use drugs

- Idiosyncrasy

Abnormal responses to a drug due to genetic (heriditory) abnormality. **Rapid acetylators** show **therapeutic failure** while **slow acetylators** show **toxicity** to a drug

- Drug interactions:

The effect of one drug on another. Takes many forms:
↑ or ↓ absorption; ↑ or ↓ protein binding; ↑ or ↓ metabolism; ↑ or ↓ excretion; ↑ or ↓ toxicity; ↑ or ↓ binding to receptors... etc

Rule: one drug is better than two; two drugs are better than three...etc

- Side effects and drug toxicity

Unwanted, untoward, undesirable, adverse reactions to a given drug
Drugs are intended to produce a specific effect. But no drug is specific in its action.
Thus, the additional, unwanted effects that are observed in addition to the desired effect of a drug, is called adverse drug effects

Types of side effects

Type A: It is the extension of known pharmacological effect of a drug
e.g. dry mouth after atropine administration

Type B: It is unrelated to the known pharmacological actions of a drug
e.g. hypersensitivity reactions to penicillins (hypersensitivity reactions or drug allergy are abnormal responses to a drug due to immunological mechanism. Previous exposure to the offending drug is required)

Pharmacodynamics:

Means mechanism of action (MOA)Drugs could either act throuh

1. Non-receptor mechanisms:

a. Physicochemical mechanisms:

- Osmotic diuretics **Urea, Mnnitol**
- Osmotic cathartics **Lactulose**
- Neutralizing effects **Antacids**
- Detergent effect **Disinfectants, Oxidizing agents**
- ↓ excitability of membranes (stabilize cell membranes) **Local anaesthetics**

b. Interaction of drug with small molecules or ions:

- EDTA binds Pb++ with high affinity → ↑ exc. **(lead poisoning)**
- Penicillamine binds Cu++ → ↑ exc.
- Dimercaprol (PAL); chelates arsenic, mercury, gold, bismuth **(detoxifying effect)**

c. Incorporation of drug into macromolecules:

Antimetabolites e.g. 5-bromouracil is similar in its structure to thymine (replaces thymine during DNA synthesis → ↑ chromosomal breakage → ↑ **anticancerous effect**)

5-fluorouracil replaces uracil during RNA synthesis → faulty protein synthesis

Ethionine replaces the a.a methionine → faulty protein

d. Enzyme inhibition (some consider enzymes being receptors to drugs):

- Cyclooxygenase inhibitors **NSAID's**
- Cholinesterase inhibitors **Neostigmine**
- Decarboxylase inhibitors **Carbidopa**
- Bacterial dihydrofolate reductase inhibitor Trimethoprim...etc

Enzyme inhibition drugs are considered as non-receptor mediated drugs

2. Receptor-mediated effects:

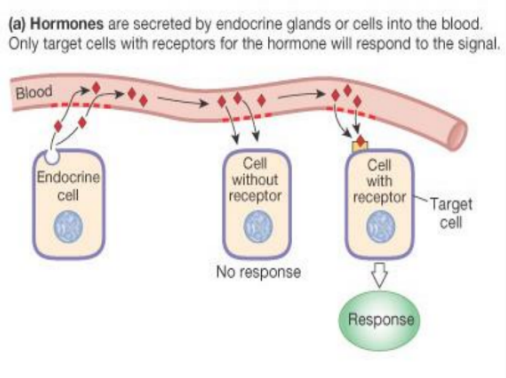
D + R ⇌ DR complex ⟶ response

Receptor: macromolecule or the component of a cell or organism that interacts with a drug and initiates the chain of biochemical events leading to the drug's observed effects

- Found **in target cells or tissues**
- **Determine the dose or concentration of drug** required to form a significant no. of drugreceptorcomplexes
- No. of receptors may **limit maximal effect** a drug may produce
- Mediate effects of agonists and antagonists
- Responsible for **selectivity** of drug action

• Size, shape, electrical charge of drug determines binding to a receptor

• Changes in a drug's chemical structure can alter the affinity for the receptor where therapeutic and toxic effects may be altered



Rational Drug Design

- Drugs are designed **based on the structure of the receptor site**
- Computers help us do this (match drug to receptor site to increase selectivity)

Lock and key theory 🔐

states that the drug structure should be **complementary** to the receptor

Binding of D to R requires that:

- Both D and R should be **close enough** to each others
- The R has to be **complementary** in it's chemical structure to the D
- Binding of the D to the R should be **reversible**

The interaction of D with R depends on:

- Chemical **structure** of D and R
- Sites of loss , Not all the bioavailability fraction of the dose that reach circulation will reach the site of action ,the drug may interact with proteins (albumin), nucleic acids, melanin, glycosaminoglycans...etc)
- Intermolecular binding forces

Binding forces between D & R:

- Van der Waals:

The **weakest** bond N.....N

The **commonest** (most universal) bond between the D & R

Close approximation between the D & R is required

The R chemical structure should be complementary to the D

- Hydrogen bond:

Stronger than Van der Waals, **Reversible** O H.....O=

Occurs when a hydrogen connects 2 oxygens or 2 nitrogens N H.....N=

- Ionic bond:

Stronger than hydrogen bond, **Reversible**

Occurs between ions of **different charges** Na+-..... -Cl-

- Covalent bond:

Irreversible ,**The least common** bond between the D & its receptor

The strongest bond; **energy is required** to break it down

Occurs when the D and the R share a pair of electrons

Three aspects of drug-receptor function:

1. Receptors determine the quantitative relation between drug concentration and response

- This is **based on receptor's affinity** to bind and it's abundance in target cells or tissues

- Drug response depends on:

Affinity of drug for receptor

Drug's efficacy(degree to which a drug is able to induce maximal effects)

2. Receptors (as complex molecules) function as **regulatory proteins** and components of chemical signaling mechanisms that provide targets for important drugs

3. Receptors determine the **therapeutic and toxic effects** of drugs in patients

Major receptor families:

1.Ligand-gated ion channels

- Responsible for regulation of the **flow of ions** through channels across cellmembranes

- Regulated by **binding of a ligand to the channels**, e.g. the nicotinic receptors, in which the binding of the acetylcholine results in sodium influx and the activation of contraction in skeletal muscle

2. G protein-coupled receptors

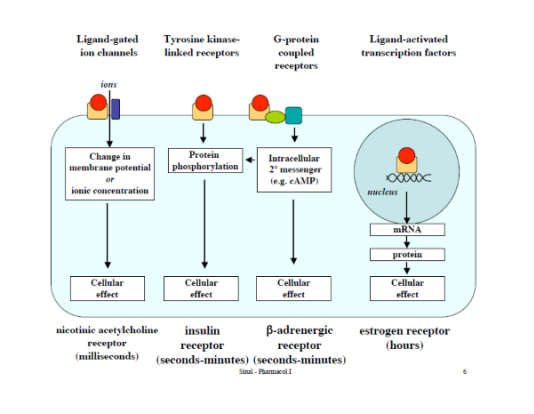
Receptors on the **inner face of the plasma** membrane regulate or facilitate effector proteins through a group of guanosine triphosphate (GTP) proteins known as Gproteins (transmembrane proteins), e.g. Some hormones peptide receptors and neurotransmitter receptors (e.g., adrenergic and muscarinic receptors) depend on the G proteins that mediate their action on cells

3.Enzyme-linked receptors

- Binding of the ligand to the **extra cellular domain** activates or inhibits the **related cytosolic enzyme**
- The most common are the receptors that have a tyrosine kinase activity as part of their structure, in which the binding results in phosphorylation of tyrosine residues of specific protein
- The addition of phosphate group **can modify the 3D** structure of the target protein, and so resulting in molecular switch (cellular effect)

3. Intracellular receptors

- In this family the **ligand must diffuse** into the cell to interact with the receptors
- The ligand must have sufficient lipid solubilities to be able to move across the target cell membranes
- The best example being the steroids hormones. In which the activated ligand-receptor complex migrate to the nucleus, where it binds to a specific DNA sequences, resulting in regulation of the gene expression.



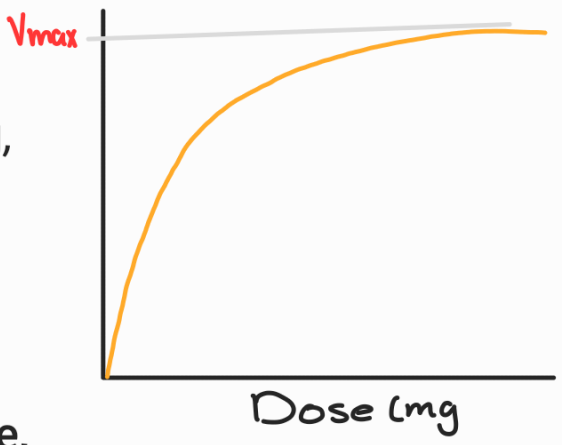
2nd messengers

involved in mediating effects of different drugs include:
cAMP, cGMP, DAG, Ca++ , ITP (IP3)...
Why we don't give the second messenger directly to the patient instead of the ligand? Because it is **not specific**, it will go to different tissues and do different responses.

Quantitative studies of drug action

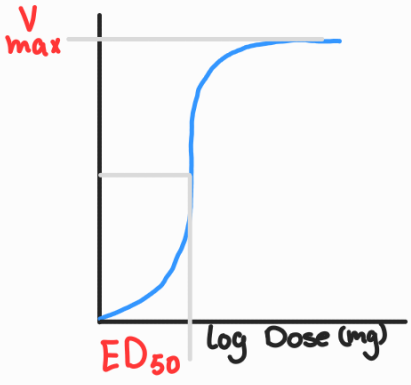
Dose response curves:

- Graded dose-response curves



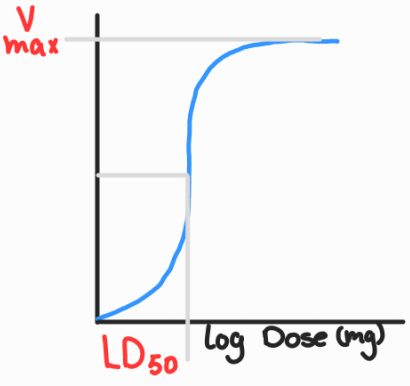
measure the effect of a dose of certain drug, to a response to certain tissue.
When we **increase the dose,**
the response increases.
However, at specific point the response will **stop increasing even if we increases the dose,** this point is called Vmax (maximal response)
Also known as **efficacy or intrinsic activity.** It is important in pharmacology

- the v max should be in the therapeutic level.. **If not ,it will be toxic.**
- What is the importance for those studies? I can know the suitable dose , for example, if the Vmax for a drug occurs within 10 grams, there's no need to give the patient 15 grams; because there will not be a response and may cause side effects.



ED50 (effective dose) whereas
50% of the response is done by the dose.
(this for tissues of animals not human).

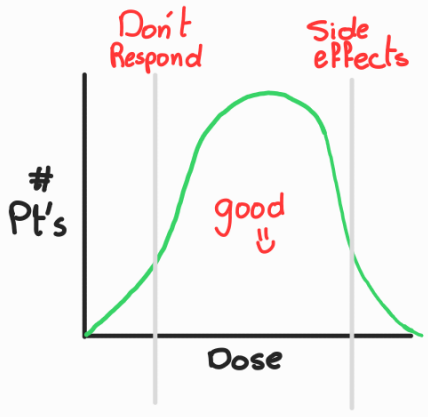
the dose which**causes 50% of deaths in animals.**
We call it **LD50**(lethal dose).
In humans the same curve will be used but it measures the side effects.
Death is considered the most severe side effect to any drug



- Quantal dose response curves

This is a normal distribution for dose response in humans.

Most people will have the required dose, also few people will have side effects or don't respond to the drug.



The distance between ED50 and LD50, **the farther away it is, the safer the drug is.**

Therapeutic index (TI):

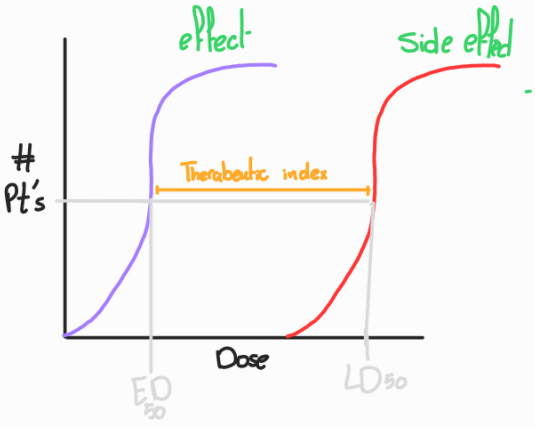
A measure of the safety of drugs

TI = LD50/ED50

4 = 400 / 100 **the safest**

1 = 100 / 100

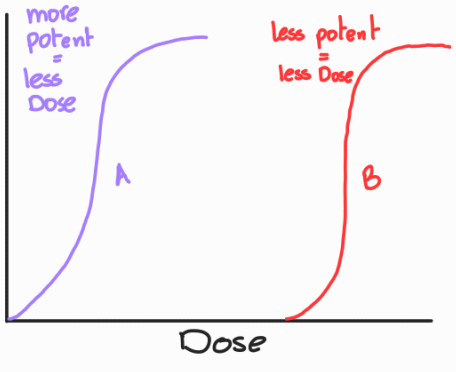
The larger the TI the more safe is the drug



- Potency:

A term used whenever we compare the activity of **two drugs** producing the **same effect**

Defined as the dose of one drug necessary to produce a specific response as compared to a second drug producing the same effect



- Affinity:

The ability of a drug to form a stable complex with the receptor.

Evaluation of drug safety:

1. **Therapeutic index (TI)** (LD50/ED50)
2. **Margin of safety** (LD0.1/ED99.9) **(should be more than 1)**

A ratio of more than 1 means that the given dose is effective in > 99% of people and producing death or side effects in < 1% of people

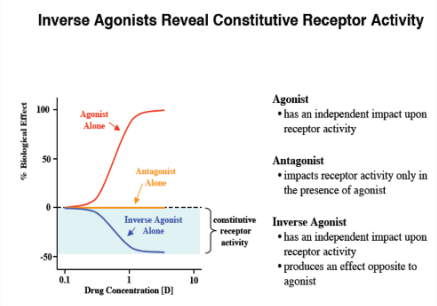
3. **Protective index (PI)**

Considered the best measure to assess safety of drugs since most drugs produce side effects in doses lower than those which produce death

$$PI = \frac{\text{ED50 producing side effects}}{\text{ED50 producing desired effect}}$$

The larger the PI the better the drug

PI of 1 means that the dose which produces the desired effect in 50% of pt's still produces side effect in 50% of them



Types of drug-receptor interactions:

1. Drug agonism:

- Agonist (full agonist):

A drug that interacts with a **specific receptor** and produces maximum response(strong agonist produces Vmax with low R occupancy; weak agonist has low efficacy but reaches Vmax with high R occupancy)

- Partial agonist

A drug that has **reduced efficacy** but maximum potency and high affinity

- Agonist-antagonistic agonists

A drug which **has both agonistic and antagonistic** activities

- Inverse agonist

A drug that produces an **effect opposite to agonist**

A receptor which is capable of producing its biological response in the **absence of a bound ligand** is said to display **"constitutive activity".**
The constitutive activity of receptors may be blocked by inverse agonist binding.
Mutations in receptors that result in increased constitutive activity underlie some inherited diseases, such as precocious puberty (due to mutations in LH receptors) and hyperthyroidism (due to mutations in TSH receptors)

Addition: 2 drugs producing **similar response** given together result in a final response **equals to the sum** of the response of each drug (1+1=2)

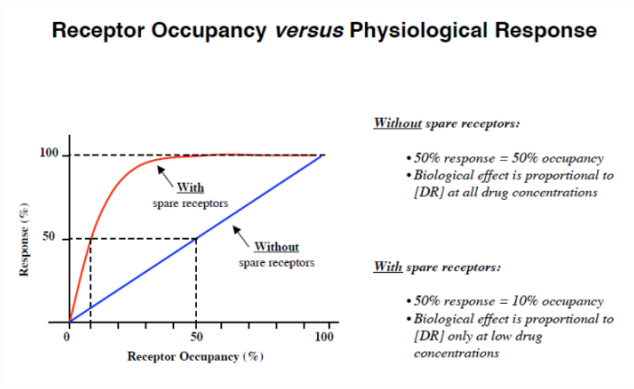
Synergism: two drugs producing **similar response** given together result in a final response **greater than the sum** of the response of individual drugs (1+1=3 or 5...)

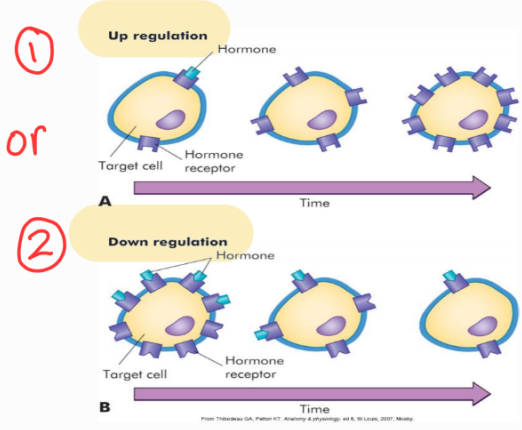
Potentiation: 1 drug producing **no response** given with **another** producing a **specific response** results in an **increase in the final response** of the second drug (0+1=2 or 5...)

Spare receptors:

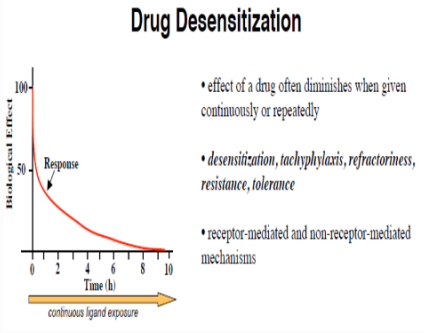
Some agonists may lead to 50% of response with less than 50% of the receptors bound (receptor occupancy).
The pool of available receptors exceeds the no. required for a full response e.g. hormones (insulin); neurotransmitters (E; NE)

(when these receptors are used for long period of time, they get damaged and spare receptors take place or comes in charge)





type 2 diabetes they have high insulin level in blood high, they have hyperglycemia, they have insulin resistance, the major mechanism is downregulation.
Now we have downregulation,
how can we solve it ? By using antagonist or invert agonist



2. Drug antagonism:

A pure antagonist is a drug which binds a specific receptor **producing no effect or response** , **but** if given with an agonist it reverses the effect of the agonist

It may take many forms:

a. Physiologic antagonism:

Sympathetic vs parasympathetic

b. Antagonism by neutralization:

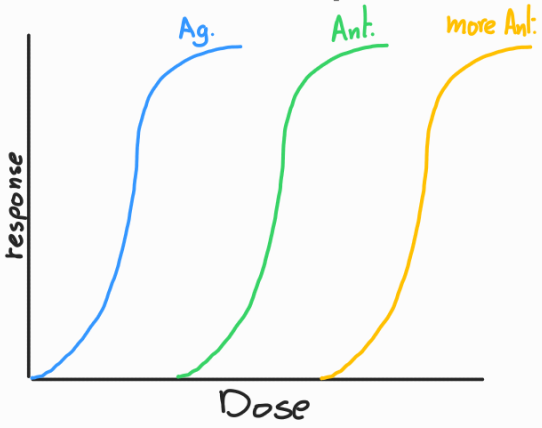
Applies whenever two drugs given together form an inactive complex

c. Pharmacologic antagonism: 2 major types

1. Surmountable antagonism (competitive; equilibrium; reversible)

Characteristics of competitive antagonism:

- Both Agonist and antagonist **compete directly for the same receptor** or even site, **reversible**
- ED50 of agonist ↑ in presence of antagonist (affinity ↓ and potency=relative affinity ↓)
- No change in total # of receptors
- No change in Vmax
- Dose-response curves are shifted to the right



2. Unsurmountable antagonism: 2 types

- Noncompetitive=uncompetitive=irrevers.

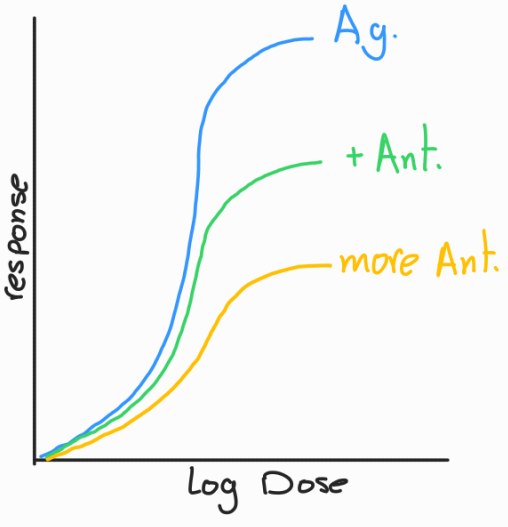
Characteristics of noncompetitive antagonism:

- Both Agonist and antagonist act on different sites of a given receptor or even different receptors, Irreversible
- ↑ dose of agonist produces no pharmacological response
- Vmax ↓ with increasing dose of antagonist
- Results in no change in the ED50 of agonist (no change in affinity or potency) but results in ↓ in Vmax
- Total # of receptors ↓
- Results in downward shift in the Dose-response curves

NOTE from the Doctor: Differences between Blockers vs antidote vs antagonists

BLOCKERS	ANTAGONIST	ANTIDOTE
Definition: drug that reverses the action of another drug used normally in your body.	A pure antagonist is a drug which binds a specific receptor producing no effect or response.	Definition: drug binds to another drug inactivating it helping its excretion by a non-receptor mechanism.
Example: epinephrine and norepinephrine produce certain actions of the sympathetic system, Beta blockers will reverse the actions by receptor mediated mechanism.	Example: atropine to treat bradycardia(slow heart rate)-additional information-.	Example: chelation (as we took previously).

- NOTES: epinephrine and norepinephrine are ENDOGENOUSLY produced substances.
- antagonist must be receptor mediated.
- Beta blockers are considered antagonists.(receptor mediated)
- They are named blockers because in addition of blocking exogenous substances, they block endogenous substances.
- ALL Beta blockers are antagonists, but not all antagonists are beta blockers.



.. ادعولنا