General pharmacology #G3FR_1

A- Pharmacokinetics

1- Absorption

Definition Passage of drugs from site of administration to *systemic circulation* the mechanism of drug absorption follows mechanisms of drug movement through biological membrane ***which include***:

A) Passive diffusion:	B) Facilitated diffusion:	C) Active transport	D) Endocytosis and exocytosis:
The most common and most important mechanism, it includes: a. Rapid movement of ***lipid-soluble*** drug across the cell membrane b. movement of ***water-soluble*** drugs across the aqueous channels "*water pores*"	No energy is required as the drugs are carried to inside of the cell ***according to the concentration gradient*** by: a. Carrier protein b. Drug transporter	Energy is required because the drug movement may be ***against the concentration gradient*** by: a. Drug transporter b. P-glycoprotein drug transporter extrudes drugs outside the cells, and it is *responsible for drug resistance*	occur by drugs *of* ***high molecular weight***. The drug binds to the cell membrane, dips in and enveloped by the cell membrane, a tear in the cell membrane allow the drug to move inside/ outside the cell. The tear is healed immediately

Factors affecting absorption

A) Factors related to the patient:

1- Route of administration

I.V. and inhalation >I.M.> S.C. >Oral > Topical

2- Absorbing surface

- ***Vascularity***: Alveoli> Skeletal ms > S.C. tissue
- ***Surface area***: Alveoli >Intestine> Stomach
- ***Pathological conditions***:
  Diarrhea & malabsorption ➡⬇ oral absorption

3- Systemic circulation

- H.F.& shock ➡⬇ absorption ➡ oral and I.M. routes are not suitable

4-Specific factors

Intrinsic factor is essential for vitamin B12 absorption.

5- Co-administration of other drugs & food

- S.C. adrenaline (added to local anesthetics) ➡ V.C ➡⬇ absorption of local anesthetics ➡ longer duration of action of local anesthetics.
- Ca^{+2} (e.g. in milk) ➡⬇ oral absorption of tetracyclines (antibiotics)

B) Factors related to the drug:

1- Water & lipid solubility

- Both are needed for absorption
- Completely water-insoluble compounds aren't absorbed *e.g.* **barium Chloride**
- ⬆ lipid solubility ➡ ⬆ absorption (⬆ lipid/water partition coefficient)

2- Ionization

- Non-ionized (uncharged) ➡ better absorption.
- Depends on ***pKa of the drug*** and ***pH of the medium***.
- Quaternary ammonium compounds ➡ ionized ➡ poor absorption.
- Streptomycin has high **pKa** ➡ always ionized ➡ not absorbed orally

3- Valency

Ferrous iron (Fe^{+2}) is absorbed better than ferric iron (Fe+3).

4- Nature

Inorganic compounds (small particles) > organic compounds (large particles).

5- Pharmaceutical preparation

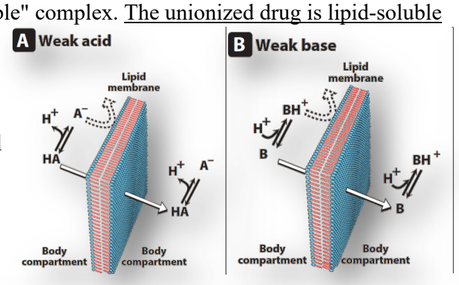
- **Dosage form**: solution > suspension > tablet.
- Shape, size of particles,
- rate of disintegration and dissolution of tablets.
- Excepient (fillEr): Ca^{+2} salts ➡⬇ oral absorption of tetracyclines

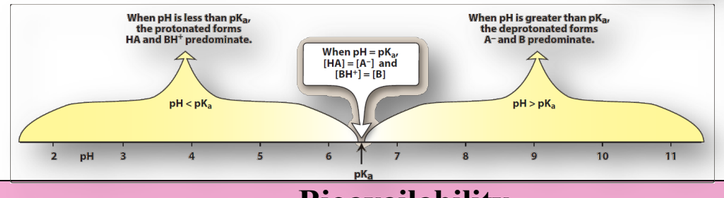
Passive diffusion

Definition The most important means by which drugs are absorbed from sites of administration & distributed within the body. It depends mainly on: • Lipid solubility • Ionization of the drug

1- Ionization of drug:

- The charge of ionized drug attracts water with formation of water-soluble "lipid-insoluble" complex. The unionized drug is lipid-soluble
- A very large percentage of the drugs in use are *weak acids* or *weak bases.*
- *Weak acids* are *unionized* when *protonated* "bind hydrogen" $HA \leftrightharpoons A^- + H^+$
- *Weak bases* are *unionized* when *unprotonated*. "loss hydrogen" $BH^+ \leftrightharpoons B + H^+$
- For weak acid or weak bases: **pKa – pH = Log protonated/unprotonated**
- **pK_a** is that pH at which the concentrations of the ionized and unionized forms are equal
- **pK_a** is specific for each drug and can be obtained from pharmacokinetic tables.
- The lower the pH relative to the pK_a, the greater will be the fraction of drug in the protonated form so, weak acid are unionized while weak bases are ionized.
- **So**, more weak acid will be unionized "lipid-soluble form" at acid pH, **whereas** more basic drug will be unionized "lipid-soluble form" at alkaline pH





2- Examples:

Aspirin "acid" has **pKa** =3.5 and **pH** in the stomach =2.5 • pKa – pH = Log protonated/unprotonated So ➡ 3.5-2.5 = 1 = log10/1

• So, aspirin is more protonated "unionized" and more lipid-soluble in the stomach.

Pyrimethamine "base" has **pka** = 7 and **pH** of small intestine= 8 • pKa – pH = Log protonated/unprotonated. So, ➡ 7- 8= -1 = log1/10

• So pyrimethamine is more unprotonated, unionized and more lipid-soluble in *small intestine*.

3- Clinical importance of pKa:

1-**GIT**: Aspirin "acidic drug" is mostly non-ionized in the empty stomach □ crosses the cell membrane of gastric mucosa cells
In *gastric mucosal cells* the **pH** is *alkaline*, so aspirin becomes ionized "lipid-insoluble" and cannot cross the cell membrane ➡ trapping in gastric mucosal cell ➡ death of these cells increased risk of **"peptic ulcer".**

2- **Kidney**: In drug poisoning, renal elimination can be enhanced by changing urinary **pH** to increase drug ionization, decrease lipid solubility, and inhibit tubular reabsorption.

• *Alkalization* of urine (to increase urine pH above drug pKa) is useful in acidic drug poisoning *e.g.* aspirin and phenobarbital.
• *Acidification* of urine (to decrease urine pH below drug pKa) is used in basic drug poisoning e.g. amphetamine

4- Conclusion:

• Absorption of drugs is mostly by simple diffusion through lipid membranes.
• Ionized form of the drug is water-soluble and cannot pass lipid membranes except through water filled pore which is too narrow to allow large molecules to pass.
•Non-ionized form of the drug is lipophilic and can easily cross lipid membranes.

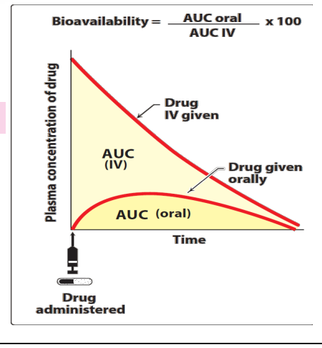
Bioavailability

the percentage of drug that reaches the systemic circulation and becomes available for biological effect
It determines the extent of drug absorption.

$$Bioavailability = \frac{Area\ under\ the\ curve\ \text{"AUC"}\ after\ oral\ route}{Area\ the\ curve\ \text{"AUC"}\ after\ IV\ route} x100$$

Factors affecting bioavailability:

1- Factors affecting drug absorption "see before"
2- 1st pass effect "pre-systemic metabolism": metabolism that occurred to drugs before reaching systemic circulation *types*:
Hepatic: nitroglycerin and propranolol
Intestinal: estrogens are extensively metabolized in their 1st pass through intestinal wall
Pulmonary nicotine is partially metabolized in lung



Extraction Ratio (ER) & Hepatic 1st Pass Effect

the percentage of the drug removed from the blood during its passage through the organ. $ER = \frac{CL\ liver}{Q}$

• high hepatic ER = high hepatic 1st pass effect =low oral bioavailability
CL_{liver} : hepatic clearance of the drug. Q: hepatic blood flow (normally about 90 L/h in a 70-kg person)

Applications of hepatic 1st pass effect and hepatic ER:

1- Drugs with high hepatic ER (extensive hepatic 1st pass effect), *e.g.* nitroglycerine, have low bioavailability.
2- Extensive 1st pass effect can be overcome by:
• Administration of the drug by routes other than oral route *e.g.*sublingual and parenteral route. • Increasing the dose.
3- extensive hepatic 1st pass metabolism with certain drug may result in toxic metabolites e.g. lidocaine ➡ convulsion *so*, not orally
4- Drugs with high ER will show marked variations in bioavailability between individuals even if given in the same doses.
This can be explained by: - The differences in hepatic function and blood flow.
- Drugs can bypass hepatic 1st pass *e.g.* in hepatic cirrhosis with portosystemic shunting ➡⬆⬆ bioavailability.
5- 1st pass effect may be desirable as in case of inactive prodrugs *e.g.* enalapril.

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2- Distribution

After absorption, the drug is distributed through 3 body compartments:

Vascular compartment	Vascular and interstitial compartments	Vascular, interstitial and intracellular compartments
Small volume of distribution	Moderate volume of distribution	Large volume of distribution
hydrophilic	hydrophilic	lipophilic
most of the drug is ionized	lesser degree of ionization	non-ionized
lipid/water partition coefficient is low	lipid/water partition coefficient is low	lipid/water partition coefficient is high
4 liters m 70kg person	14 liters in 70kg person	40-42 liters in 70kg person
heparin	neostigmine	barbiturates

Factors affecting distribution of drugs

1-**Blood flow (perfusion)**: Amount of drug delivered to particular organ depends on blood flow to the organ ⬆blood flow ➡⬆distribution
2-**Lipophilicity (diffusion):** ability of the drug to diffuse across cell membranes depends on lipophilicity⬆ lipophilicity ➡⬆ distribution
Characteristic of Lipophilic drug: 1- Well-absorbed orally. 2- Usually subjected to hepatic 1st pass effect.
3- Eliminated mainly by liver (hepatic elimination). 4- Crosses blood-brain, and placental barriers.
3- **Plasma protein binding (PPB):** drug in blood exists in *two forms:*
- *PP bound form*: inactive, non-diffusible, and not metabolized or excreted.
- *Free form*: active, diffusible, and can be metabolized or excreted.
The two forma exist in *equilibrium* between bound and free part
Characteristics of drug with high PP binding:
1- **PP** hound fraction cannot be eliminated and acts as **reservoir**.
2- A drug with higher affinity can displace another one with less affinity ➡⬆its free concentration and action "drug-drug interactions".
3- Displacement from PP is clinically important when drug has **high PP capacity & small Vd** (most of drug is present in the circulation).
. So minimal displacement ➡ large increase in the free part ➡ toxicity. **Example**: **aspirin** displaces **warfarin** (PPB: 99%) ➡ bleeding
4- binding to tissue constituents "tissue affinity": Affinity of certain drugs to bind to specific cellular constituent
e.g. • Chloroquine *is concentrated in* liver. • Iodides *concentrated in* thyroid and salivary glands.

Blood-brain harrier (BBB)	Placental barrier	Redistribution
• Only lipid-soluble non-ionized drugs can pass blood-brain barrier. • Inflammation (meningitis) ➡⬆permeability of BBB (concentration of penicillin & cephalosporins in the CSF is 0.5- 1 % increase up to 5% in meningitis	Drugs that can pass placental barrier may cause: • During pregnancy ➡Teratogenicity, embryotoxicity. • During labor ➡ Neonatal asphyxia, neonatal jaundice (Kernicterus).	• Occurs with highly lipid-soluble drugs as thiopental. After initial distribution to CNS, thiopental redistributes to less perfused tissues e.g. skeletal muscle and fat. ending its action. • Importance: repeated administration ➡ Tissue saturation ➡ CNS accumulation ➡ Toxicity

Volume of Distribution Vd

it's a hypothetical (apparent) volume of body fluids that would accommodate the total amount of the drug in the body in concentration equal to that of plasma.

$$Vd = \frac{Amount\ of\ the\ drug\ in\ the\ body}{plasma\ concentration}$$

Importance of Vd

1- **In treatment of drug toxicity**:
• *Dialysis* is not useful for drugs with *high Vd* (most of the drug is in the *tissues*).
• *Hemodialysis* is useful for drugs with *low Vd* (most of the drug is in the *blood*).
• *Peritoneal dialysis* is useful for drugs with *moderate Vd*.
2- *Vd* of a drug is directly proportionate to *half-life* of the drug: $\mathbf{t\frac{1}{2} = 0.693\ Vd/Cls}$
3- calculation of the **loading dose of a drug = (desired plasma Css) X (Vd).**
4- calculation of the **corrective dose of a drug = (desired plasma Css - achieved plasma level) X (Vd).**

(Cls = drug clearance, Css = drug steady state plasma concentration)

3- Biotransformation (Metabolism)

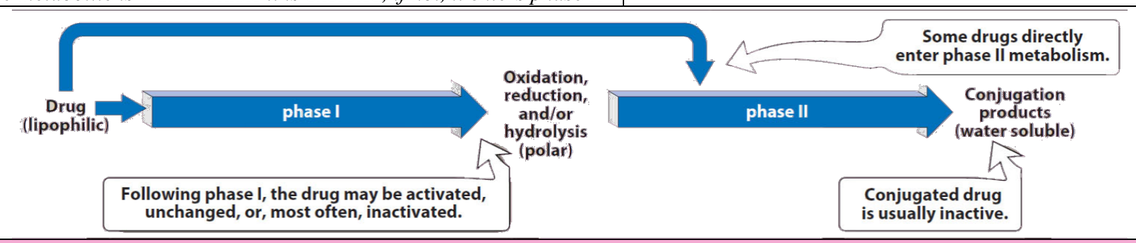
chemical alternation of drugs to convert (active, lipophilic, non-ionized) *drug* to (inactive, hydrophilic, ionized) *metabolites* ➡ easily excreted • Drug metabolism occurs mainly in the *liver.*

Consequences of drug metabolism

1- Convert *active* drug to inactive *metabolite* "most drugs".
2- Convert *inactive prodrug* into *active drug* e.g. enalapril ➡ enalaprilat (active) & prednisone ➡ prednisolone (active).
3- Convert *active drug* to *active metabolite* e.g. codeine ➡ morphine.
4- Convert *drugs* to *toxic metabolites* e.g. halothane & paracetamol ➡ toxic epoxides which are conjugated with glutathione. *So,* Glutathione deficiency may precipitate paracetamol or halothane hepatotoxicity.

Types of biotransformation reactions

Phase I (functionalization) reactions:	Phase II (biosynthetic "conjugation") reactions:
- *Phase I reactions include:* oxidation, reduction *and* hydrolysis - *The* most important *reaction is* oxidation *by Cytochrome* P_{450} - *Result in conversion of* active drug *to* inactive metabolite *(sometimes convert the* prodrug *to* active drug*)* - *If the metabolite is* water soluble *it is* excreted*, if not, it enters phase II*	- Conjugation of the drug or its metabolites with endogenous substance *e.g.* glucuronic acid, sulfate, glutathione, amino acids, or acetate to form non-toxic, highly polar (ionized), water-soluble and rapidly eliminated conjugates.



Metabolizing enzymes

A- Microsomal enzymes	B - Non-microsomal enzymes:
A-Cytochrome P_{450} oxidases and their family 1 & subfamily 2 CYP2C9 B- Glucuronyl transferases for conjugation	Dehydrogenase, esterases (plasma) & xanthine oxidases (cytoplasm)

Factors affecting biotransformation:

1. Physiological changes (age & sex). 2. Pathological factors (liver cell failure!).
3. Pharmacogenetic variation in metabolizing enzymes e.g. slow and fast Acetylators 4. Enzyme induction & enzyme inhibition

Enzyme induction	Enzyme inhibition
Many drugs are able to induce the activity of microsomal enzymes resulting in increased rate of metabolism of other drug metabolized by microsomal enzymes **as well as** their own metabolism	Many drugs inhibit activity of microsomal enzymes resulting in decreased rate of metabolism of other drugs metabolized by microsomal enzymes so, potentiate their pharmacological actions.

Consequences

1- Failure of drug action: • Rifampicin "enzyme inducer" enhance metabolism of progesterone and warfarin. 2- Tolerance e.g. phenobarbitone increase its own metabolism "Auto-induction" 3- Increase metabolism of endogenous substrate e.g. phenobarbitone may be used to enhance elimination of bilirubin in physiological jaundice.	1- Exaggerated pharmacological actions. 2- Increased duration of action and half-life of some drugs.
4- Drug interactions: • Rifampicin enhances metabolism of warfarin, and may lead to failure of contraception "enhance metabolism of progesterone" • Antiepileptics increase the metabolism of each other if combined • Prolonged use of enzyme inducers may produce rickets or osteomalacia due to increased metabolism of vitamin D. • Enzyme induction is reversible. It occurs over few days and passes off over 2 - 3 weeks after withdrawal of inducer.	3- Drug interactions.

Example

• **P**henytoin • **P**henobarbitone. • Rifampicin • Nicotine. • Carbamazepine	• **C**iprofloxacin • **C**imetidine • **CC**P “Contraceptive pills” • Allopurinol • Erythromycin • Na^+ valproate

General pharmacology #G3FR_3

4- Excretion of Drugs

1-Renal "main way "

A) Glomerular filtration:

• Free drug molecules whose size is smaller than the glomerular pores are filtered into Bowman's capsule

B) Tubular secretion:

• Occurs primarily in the PCT by energy-dependent active transport systems.
• *Active secretion* occurs through:
- *acid carrier* e.g. for penicillin, probenecid & salicylic acid
- *basic carrier* for amphetamine & quinine.

C)Tubular reabsorption:

• *Lipophilic drugs* maybe reabsorbed back to systemic circulation.
•*Alkalization of urine* by NaHC03 keeps acidic drugs ionized ➡⬆excretion
• *Acidification of urine* by ascorbic acid "vitamin C" or ammonium chloride ➡ionization of weak bases ➡⬆secretion

2- Milk

Important in lactating mothers

Examples of drugs contraindicated during breast feeding:

1- Antibiotics*: Chloramphenicol, tetracyclines & sulfonamides.*
2- CNS drugs*: Narcotics, benzodiazepines, alcohol & nicotine.*
3- Laxatives*: Cascara & Senna.* *4-* Corticosteroids*: suppress baby's growth & immunity.*
5- Bromocriptine*: suppresses lactation.* *6-* Sex hormones*: CCP suppress lactation.*
• To decrease risk to infants, lactating mothers should take drugs immediately after nursing or 3-4 h before next feeding.
• Ph of milk is more acidic than that of plasma ➡basic drugs accumulate in milk. Also, milk contains more fat which leads to retention of lipid-soluble drug e.g. cytotoxic drugs, metronidazole, morphine and laxatives.

3- Bile

• Drug excreted in bile may undergo enterohepatic cycle,➡ longer duration of action
e.g. doxycycline & azithromycin
• Biliary excretion of drugs increases their efficacy in treatment of intestinal and biliary diseases

4- Lungs

e.g. volatile anesthetics.

5- Sweat

e.g. rifampicin.

6- Saliva

e.g. iodides.

Parameters of Elimination

1- Kinetics Orders

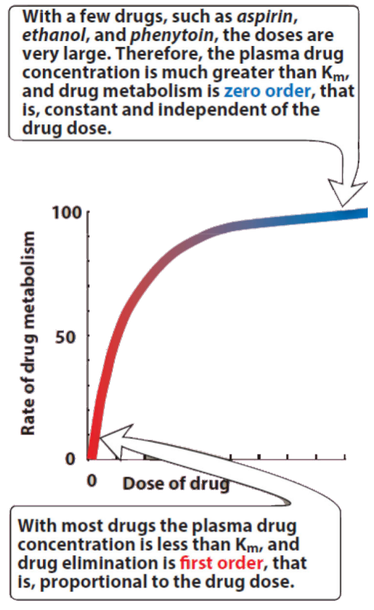
	First order kinetics	Zero-order kinetics
Rate of elimination	**Directly proportionate** to the blood concentration of drugs i.e. constant **percentage** of the drug is eliminated per unit of time	**Constant** i.e. constant **amount** of drug is eliminated per unit of time.
t½	**Constant** With ⬆ concentration	**Not constant** "increase with ⬆ concentration"
Css (steady state concentration)	• Repeated dosing increases drug concentration and accordingly the rate of elimination increases till the rate of administration equals the rate of elimination. At this point Css is reached. • Css is directly proportionate to the dose (⬆dose ➡⬆ Css) • After 4-5 t½ more than 95% of Css is reached	•No Css is reached by repeated dosing •Any change of the dose may cause toxicity.
Example	**Most drugs** obey 1st order kinetics.	**large doses** of aspirin, phenytoin & ethanol

Saturation kinetics

Some drugs follow 1st order kinetics in small dose and zero order kinetic at large doses i.e. the elimination mechanism is said to be saturated "**saturation kinetics**".

Importance of saturation kinetics

1. Modest change in dose or bioavailability may cause unexpected toxicity.
2. Drug-drug interactions are common.
3. Drugs obeying saturation kinetic: phenytoin and aspirin.
4. These drugs need monitoring of their plasma levels to avoid toxicity



2- Elimination Half-life t½

It is the time needed to reduce the plasma concentration of the drug to half the initial concentration

"the time required for drug concentration to be changed by 50%" $t\frac{1}{2} = 0.693 \text{ Vd/CLs}$

Factors affecting elimination t½

1- State of eliminating organs i.e. liver & kidney function.
2- Delivery of drugs to the eliminating organs (high Vd limits elimination)

Importance of elimination t½

1- it determines the dosage interval (T).
• If T = t½
• *If T* < t½ ➡ drug *accumulation* may occur.
• *If T* > t½ ➡ drug *concentration decreases* between doses.
2- It indicates time required to attain Css "*about 4-5* t½:
• lf the drug is administered every " t½" ·
•After the 1st " t½", drug concentration reaches 50% of the final Css.
•After the 2nd " t½", drug concentration reaches 75% of the final Css.
•After the 3rd " t½" drug concentration reaches 87.5% of the final Css.
•After the 4th & 5th "t½", drug concentration reaches 93.75% & 96.87% of the final Css.
• So, if the drug is given each t½ Css is reached after 4-5 t½
3- If t½ is very short (seconds or minutes), the drug should be given by IV infusion e.g. dopamine, dobutamine. esmolol.
4- If t½ is very long the drug should he administered in a loading dose to reach the desired Css rapidly "in emergency cases", followed by maintenance dose to maintain the desired Css.

How to prolong duration of action of drugs

1- Delay absorption:
• Use sustained-release (SR) preparations.
• Add vasoconstrictor e.g. adrenaline to local anesthetics
• Use S.C. pellet implantation.
• Add oil to vasopressin.
• Use moderately soluble preparations e.g. protamine zinc insulin suspension
2- *Decrease metabolism*: use enzyme inhibitors.
3- *Decrease excretion*: probenecid ➡⬇ renal secretion of penicillin.

3- Systemic Clearance (CLs)

It is the volume of fluid cleared from the drug per unit of time.
CLs = Rate of elimination / Drug concentration
• Systemic clearance is equal to the sum of individual organ clearances i.e. clearance by liver, kidney, lungs.
CLs = renal clearance (CLr) + non-renal clearance (CLnr)

Factors affecting drug clearance

1- Blood flow to the clearing organs (directly proportional).
2- Activity of clearing processes e.g. hepatic enzymes, glomerular filtration secretory processes (directly proportional).
3- Plasma protein binding of the drug (inversely proportional).

Significance of clearance

1- Calculation of the maintenance dose ***(MD) = CLs X Css.***
2- The dosing regimen of drugs eliminated by glomerular filtration can he guided by creatinine clearance e.g. dosing of gentamicin
• If kidney function is normal (creatinine clearance "CrCL" = 120 ml/min ➡ dose is 80 mg 3 times/day.
• If kidney function is impaired, you can **reduce the dose** or increase the dosage interval according to Cr CL:
• If CrCL = 60 ml/min give half the usual dose (40 mg 3 times/day)
• If CrCL = 30 ml/min give half the usual dose (20 mg 3 times/day)
Or give the usual dose every 32 hours

Notes

• **Loading dose**: dose required to achieve desired plasma concentration (desired Css) rapidly, followed by routine maintenance dose
Loading dose = Vd x desired Css
• **Maintenance dose**: The dose given to maintain the desired Css
Maintenance dose = clearance x desired Css
• **Changing the dose** does not change the time needed to reach Css but changes Css.
• **Increasing dosing frequency** reduces the amplitude of swings and troughs in drug concentration but the value of Css is constant

General pharmacology #G3FR_4

B- Pharmacodynamics

Definition Pharmacodynamics of a drug includes its pharmacological actions and their mechanism of action

Signal transduction system

Drug + receptor ➡ D/R complex ➡ response

Types of receptors

1-Ligand-gated ion channel receptor

receptors stimulation results in opening of certain ionic channels.
- Ach + Nicotinic receptor ➡⬆ Na^+ influx ➡ depolarization
- GABA + $GABA_A$ receptor ➡⬆ Cl^- influx ➡ hyperpolarization ➡ inhibition.

2-G. Protein-Coupled receptor (GPCR)

The agonist binds to the receptor that activates G protein ➡ dissociation of α subunit ➡(+) adenylate cyclase ➡⬆ cAMP "2nd messenger"

Type of G proteins

G_s "stimulatory"	G_i "inhibitory"	G_q protein
Linked to β receptor	Linked to α_2 & M_2 receptors	Linked to α_2, & M_3 receptors
Stimulation of β receptors (Gs- coupled receptors) ➡ activates adenylate cyclase ➡⬆ cAMP ➡ activates protein kinase A ➡ Phosphorylation of proteins	Stimulation of these receptors ➡⬇ cAMP	- Stimulation of these receptors ➡ (+) phospholipase C ➡⬆ IP_3 & DAG. - IP_3 ➡⬆ Ca^{+2} release. - DAG ➡(+) protein Kinase C ➡ phosphorylation of proteins

3-Receptors linked to tyrosine kinase

Insulin has 2 components (extracellular for drug & intracellular tyrosine kinase activity)

4-Intracellular receptors

A. Hormone receptors:

Thyroid & steroid hormones pass through cell membrane ➡ bind to intracellular receptors ➡ D/R complex ➡ passes to the nucleus ➡ DNA transcription ➡ mRNA ➡ gene expression as modification of protein production

B.-Soluble guanyl cyclase (sGC)

Nitric oxide (NO) releasing agent (nitrates, nitroprusside, Ach , and histamine) ➡ NO ➡ (+) sGC in cytoplasm of smooth muscle ➡ converts GTP into cGMP "2nd messenger" ➡ (+) protein kinase G ➡ intracellular phosphorylation & smooth muscle relaxation.

Drugs act through

1-Receptor-mediated mechanism

Receptor: specific cellular structures, protein in nature, interact with either endogenous ligand or exogenous drug to mediate a physiological or pharmacological effect.
Most of receptors contain more than one binding site (usually 2), the first is called **orthostatic (or catalytic),** and the second is called **allosteric** binding site.
Drug-receptor binding: Drugs must have an appropriate composition and electrical charge to interact with specific receptor (**affinity**).

Types of drugs acting on receptors:

Agonist

A drug that binds to the catalytic receptor (**affinity**).
It has intrinsic activity i.e. produce response (**efficacy**).

Types of agonists

Full Agonist	Partial agonist	Inverse agonist
Produce maximal efficacy=**1**	• It binds to the catalytic receptor "**affinity**". • Produces less than maximal efficacy (<1) even with all receptors occupied. • It **blocks the effect of full agonists**	• Most of the receptors have variable degrees of activity in the absence agonist (**constitutive activity**) • Some drugs bind to the receptor "**affinity**" ➡ Decrease the constitutive activity **"negative efficacy"** • they inhibit the effect of the full agonists "**Inverse agonist**"
Examples		
		metoprolol on β1-adrenoceptor, famotidine in H_2 receptor, resperidone in 5-HT2 & D_2, D_3, D_4.

Antagonist

Drug binds to receptor (**affinity**), produces no response (**efficacy=0**) &prevents action of the agonist
Antagonist is the drug which has affinity without efficacy and blocks the effect of agonists

Types of antagonists

Competitive antagonist	Non-competitive antagonists	
	Irreversible	**Reversible (Allosteric)**
• The antagonist binds **reversibly** to the catalytic site of the receptor. • Can be displaced from the receptor by increasing the concentration of the agonist • Decreases **potency** but **not efficacy** of the agonist.	• The agonist and antagonist act on the same (catalytic) site, but the antagonist binds **irreversibly** (usually by covalent bond) • could not be displaced from the receptor by increasing the concentration of the agonist.	• The agonist act on the orthostatic (catalytic) site, and the antagonist acts on another site called "allosteric site". • This leads to decreased binding of the agonist to its catalytic site. • Binding of the agonist could not be enhanced by increasing its concentration.
Duration of antagonism depends on		
Relative plasma concentration of agonist and antagonist	the rate of synthesis of new receptors	the t½ of both the agonist and antagonist

2- Non-receptor mediated mechanism

1- **Drugs acting on enzymes**:
Choline esterase inhibitors: Neostigmine.
Cyclo-oxygenase inhibitors: Aspirin.
2- **Drugs act on plasma membrane**:
Digoxin inhibits membrane-bound Na^+-K^+ ATPase
3- **Drugs acting on genetic apparatus**:
Anti-cancer drugs. Antibiotics: Rifampicin.
4- **Drugs acting by physical means**:
Lubricants: liquid paraffin used in constipation.
Osmosis: osmotic diuretic (mannitol).
Demulcents: bismuth is used to protect gastric mucosa in peptic ulcer.
5- **Drugs acting by chemical mechanism**:
• Antacids neutralize HCI in peptic ulcer
• Protamine neutralizes heparin by its positive charge in heparin overdose
• **Chelation**: is the capacity of organic compounds to form inactive more water-soluble and easily excreted complex "chelate". Used in ttt of heavy metal poisoning e.g.
- EDTA: chelates lead and calcium m lead poisoning and hypercalcemia.
- Desferrioxamine: chelates iron in iron toxicity.
- Penicillamine: chelates copper in Wilson's disease

General pharmacology #G3FR_5

Dose-response relationship

Graded dose-response curve

Graph that represents increased response resulting from increasing drug concentration or dose (⬆dose ➡⬆response)
Efficacy: ability of drug receptor complex to produce response
Maximal efficacy (E. Max): The maximal response produced by the drug (the maximal value of the dose response curve)
Potency: the amount of the drug in relation to its effect.

Quantal dose-response curve

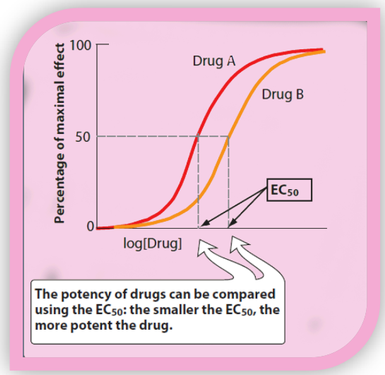
A graph of the percentage of subjects that show specific response at progressively increasing doses (⬆ dose ➡⬆ % response)

Example

- 1mg of drug A produces the same response of 5mg of drug B ➡ Drug A is more potent than drug B

- **ED_{50} (Effective Dose $_{50}$) or EC_{50} (effective concentration 50)**
The dose or concentration that produce 50% of the maximal response in graded dose response curve

- Drugs with low ED_{50} (or EC_{50}) are more potent than drugs with high ED_{50} (or EC_{50})



- **ED_{50} or EC_{50}**: the dose or the concentration that cures 50% of subjects.
- **LD_{50} (Lethal Dose 50):** the dose that kills 50% of animals in the experiment.
The drug with low LD_{50} is considered to be more toxic than the drug with higher LD_{50}.

Therapeutic Index (TI)

- The ratio between LD_{50} and ED_{50}
- **TI = LD50/ED50**
- It measures the safety of drugs i.e.
Large TI ➡ Wide safety margin & the drug is less toxic
Small TI ➡ Narrow safety margin drugs e.g. aminoglycosides, antiepileptics, theophylline, hypoglycemic agents and anticoagulants.

Therapeutic window (TW)

- The most important parameter for safety
TW = Minimum toxic dose - Minimum effective dose

e.g. TW of theophylline 8-18 = 8 mg/L

Factors modifying dose response relationship

1- **Dose**: ⬆dose ➡⬆response
2- **Age**: younger patients cannot tolerate adult dose i.e. require smaller dose

Calculation of child dose

Age method	Weight method
$\text{Child dose} = \text{adult dose} \times \frac{\text{age "years"}}{\text{age} + 12}$	$\text{Child dose} = \text{adult dose} \times \frac{\text{Weight (kg)}}{70}$

Calculation of Geriatric dose (> 60 y)

$\text{Geriatric dose} = \text{adult dose} \times \frac{3}{4}$ *or* $\frac{2}{3}$

3- **Psychological factors**: Some patients may respond to a placebo in the same way as active drug. The placebo (inert. inactive substance) may be used for psychological therapy and in control studies to exclude psychological effects of drugs
4- **Drug interactions**: the response to drug may be affected by administration of another drug
5- **Sex**:
- female may respond to lower doses of drugs. This may be explained by Smaller muscle mass and inhibitory effect of estrogen on CYP_{450}.
- Some drugs are contraindicated with pregnancy and lactation.
6- **Pathological status**: Liver and kidney disorders ➡ decreased drug elimination.

7- **Tolerance**: Gradual decrease in drug response inspite of the same dose of the drug with prolonged use (higher doses are needed to produce the same effect)

Causes of tolerance:

A) Pharmacokinetic causes:

tolerance due to ⬇drug level
1- Decreased drug absorption: frusemide tolerance due to CHF ➡ gut congestion & decreased absorption
2- Decreased delivery to site of action: frusemide tolerance in case of hypoalbuminemia.
3- Increased elimination: increased metabolism by enzyme inducers.

B) Pharmacodynamic causes:

tolerance without ⬇drug level
1- Decreased sensitivity of receptors e.g. opiates.
2- Decreased number of receptors (Down-regulation) e.g. β. Agonists.
3- Increased number of receptors (Up-regulation) e.g. H_2 blockers.
4- Depletion of neurotransmitters e.g. dopamine depletion with amantadine

Special types of tolerance:

1- Tachyphylaxis: rapid (acute) tolerance, but the same effect cannot be obtained by⬆ the dose.
2- Cross-tolerance: tolerance to one drug produces tolerance to related drugs.

Characteristics of acquired tolerance:

1- Reversible.
2- Doesn't affect all actions to the same extent (morphine ➡tolerance to analgesia & R.C depression, but not to constipation or miosis).
3- Drug dependence may follow tolerance.
4- May affect the therapeutic dose but not the toxic dose (⬇therapeutic index)

General pharmacology #G3FR_6

Adverse drug reactions

Harmful effects of drugs which may require reduction of the dose, drug withdrawal or immediate treatment.

Type A (Augmented adverse effects)

1- Drug intolerance	2- Side effects	3- Overdose	4- Toxic effect
At sub-therapeutic dose	At therapeutic dose	At higher dose> therapeutic	At very high doses
Exaggerated response to small doses of the drug." supersensitivity"	Pharmacological action occurs in every person, dose-related and predicted.	Exaggerated pharmacological action.	hepatotoxicity with acetaminophen.

Type B (Bizzare adverse effects)

A- Hypersensitivity

Non-pharmacological action, not dose-dependent, and induced by prior contact with drugs that act as antigen.

Drug Allergy

- Allergic reactions are adverse effects mediated by **immunogenic** mechanism.
- Drug allergy is **dose-independent**, unpredicted and occur in minority of patients.
- Most of drugs act as incomplete antigen or hapten.
- Cross-allergy may occur with a group of chemically related drugs.

1- Type 1 (immediate type, anaphylactic) allergic reactions	2- Type II allergic reactions	3- Type III allergic reactions	4- Type IV (delayed type or cell-mediated) allergic reactions
- IgE-mediated May be in the form of asthma, anaphylaxis, drug rash or angioedema. e.g. Penicillin. Treatment of anaphylactic shock: • Adrenaline IM. • Antihistaminic IM or IV. • Corticosteroid IM or IV.	- IgG or IgM antibodies are fixed to circulating blood cells producing complement-dependent lysis reaction. - e.g. autoimmune hemolytic anemia (methyl dopa) & Thrombocytopenia (heparin) & agranulocytosis (chloramphenicol)	- IgG -mediated. Ag-Ab complex is deposited in capillary bed. Reaction may be: serum sickness, glomerulo-nephritis (penicillin & Sulphonamides).	Mainly contact dermatitis (Sulphonamides).

B-Idiosyncrasy

Genetically mediated adverse effects e.g. favism.

Pharmacogenetic Disorders

Abnormal drug response due to genetic abnormality. Genetic abnormalities that are discovered only by the effect of drugs.

1- Acetylator status	2- Hemolytic anemia due to G6PD deficiency	3- Porphyria	4- Succinyl Choline apnea	5- Malignant Hyperthermia
• Acetylation is an important reaction in phase II hepatic metabolism. • The population is divided into slow and rapid Acetylators. • Drugs accumulate in the slow Acetylators and produce toxic effects. e.g. Isoniazid ➡ neuropathy (in slow acetylators)	G6PD deficiency ➡ hemolysis in presence of some oxidant drugs as anti-malarial, aspirin, Sulphonamides and fava beans.	phenobarbitone increases the activity of ALA synthetase enzyme ➡⬆ level of porphyrins ➡ severe neurological disturbances and may cause death.	Genetic defect in pseudocholinesterase enzyme responsible for succinylcholine hydrolysis ➡accumulation of succinylcholine ➡**Respiratory muscle paralysis and apnea.**	Genetic disorder in which skeletal muscles fail to sequester Ca^{+2} in sarcoplasmic reticulum following administration of succinylcholine and/or halothane. result in marked **muscle rigidity and fever.**

Type C (Chronic adverse effects)

1-**Tolerance**.
2- **Drug dependence**:
• **Habituation** (Psychic dependence).
• **Addiction** (Psychic & Physical dependence). Sudden stop Withdrawal syndrome.
3- **Iatrogenic diseases** (drug-induced diseases): Corticosteroids, Diabetes, hypertension osteoporosis

Type D (Delayed adverse effects)

May occur after stopping drug.
1- **Mutagenicity**: drug-induced gene abnormalities.
2- **Carcinogenicity**: drug-induced neoplasm.
3- **Teratogenicity**: drug-induced fetal abnormalities when given during pregnancy
• Thalidomide ➡ phocomelia.
• Adrenal steroid ➡ cleft palate.

Type E (End of use adverse effects)

1- **Abstinence** (withdrawal syndrome): occurs in drug-dependent persons (addict) following withdrawal of narcotics.
2- **Hypertension** following clonidine withdrawal
3- **Thromboembolism** following anticoagulant withdrawal.

Drug Interactions

Pharmacological responses that result when multiple drugs are used concurrently

Drug interactions may result in

Synergism	Summation	Potentiation	Antagonism
The combined effect is more than the sum of their separate effects	Th combined effect equals the sum of their separate effects	• A drug, when applied alone, has no effect. However, it can potentiate the effects of other agents. • example: • enzyme inhibitors ➡⬆activity of other drugs • benzodiazepines facilitate the effect of GABA at $GABA_A$ receptors.	one drug decreases the effect of another one **Types of antagonism:**

Chemical antagonism	Physiological antagonism	Pharmacological antagonism
• Neutralization: protamine & heparin • Chelation: Desferrioxamine & iron	(2 agonists + 2 Receptors ➡ 2 opposing actions) •Adrenaline ➡ bronchodilatation (β_2) & Histamine ➡ bronchoconstriction	• Pharmacokinetic antagonism (absorption & metabolism) • Pharmacodynamic antagonism (receptor block): may be competitive or non-competitive

Mechanisms of drug interaction

1- Pharmacokinetic Interactions

A- Interactions at the site of absorption (before absorption):	B- Interactions during distribution:	C-Interactions at sites of biotransformation:	C-Interactions at sites of excretion
1- Tetracyclines absorption is decreased by Ca^{+2}, Mg^{+2} and Al^{+3} containing antacids. 2- Drugs that alter GIT motility influence the rate and extent of absorption of other drugs e.g. •Anticholinergics ➡⬇Motility ➡ ⬇absorption of other drugs • Prokinetics ➡⬆ motility ➡ ⬆absorption of other drugs. 3- Drugs that change PH of the gut contents can also affect the rate of absorption of other drugs by affecting drug ionization.	1- Competition for PPB sites: see before 2- Direct interactions in plasma or tissues: • Protamine & heparin (chemical neutralization). 3- Competition/or tissue binding sites: • Increase plasma digoxin by concurrent quinidine therapy	1-enzyme inducers: • Rifampicin ➡⬆metabolism of oral contraceptives ➡ pregnancy. • Phenytoin ➡⬆metabolism of vitamin D ➡osteomalacia 2. enzyme inhibitors: • Erythromycin ➡⬇ metabolism of theophylline • Ciprofloxacin ➡⬇ metabolism of theophylline & warfarin.	1- Alkalization of urine ➡ increases ionization of acidic drugs (aspirin) ➡ decrease tubular reabsorption ➡ increases excretion (useful in treatment of toxicity). 2- Acidification of urine ➡ increases ionization of basic dugs (amphetamine) ➡ Decrease tubular reabsorption ➡ increases excretion useful treatment of toxicity. 3-Probenecid competes with penicillins for renal tubular excretion ➡ inhibit its excretion & prolongs its action.

2- Pharmacodynamic Interactions

A- Synergistic interactions:	B-Antagonistic interactions:
• Benzodiazepine-induced CNS depression is potentiated by alcohol. • Digitalis-induced bradycardia is exaggerated by β-blockers and verapamil	α-blockers, β-blockers and opiate antagonists block the effects of their agonists

3- Pharmaceutical Interactions

Incompatibilities occurring outside the body

Beneficial drug interactions

They are drug combination that; 1- Have different mechanisms of action. 2- Correct undesirable reactions of each other. **Example**: multiple drug therapy for treatment of hypertension, CHF & T.B.

nail: Ibrahim_gaafar@hotmail.com
ıcebook: https://www.facebook.com/ibrahim.ga3far
ıone & WhatsApp: +201144148853