Mechanism of Drug Action

I. Mechanisms of drug action:

1. Receptor occupation as cholinergic, adrenergic and histamine receptors, occupied by acetylcholine, adrenaline and histamine respectively
2. Interference with ion channels, some drugs act directly on ion channels and alter their function as local anesthetics act by blocking Na^+-channels.
3. Inhibition of membrane bound enzymes as Na^+/K^+ ATP-ase inhibition by digoxin.
4. Through physicochemical properties; like osmotic effect as magnesium sulphate, a laxative acts by increasing water in the faecal material and facilitate their passage through the colon, manitol acts as osmotic diuretic
5. Direct chemical reaction as the use of alkaline to neutralize gastric acid in the stomach and Chelating agents as penicillamine in heavy metals poisoning.
6. Enzyme inhibition as cholinesterase inhibition by nesostigmine and angiotensin converting enzyme inhibition by captopril.
7. Antimicrobials cause inhibition of bacterial metabolic processes as sulphonamides inhibit bacterial dihydrofolate reductase enzyme, this leads to inhibition of folic acid synthesis by the bacteria, but not affects the human which does not synthesize folic acid.
8. Carrier mechanism: some drugs act by interfering with passage of molecules across the cell membrane such as the inhibition of noradrenaline uptake by tircyclic antidepressants, carrier mechanism is important for the transport of molecules as glucose, amino acids and organic molecules.

Receptors: are protein macromolecules usually but not always situated on the cell membrane and have the ability to combine with the drug molecule, and transmit the drug effect to the inside of the cell. The drug molecule has to be similar in size, shape, chemical structure in order to combine to its specific receptor. So the receptors are important for the specific and selective action of the drug.
The presence of receptors usually indicates that there are endogenous substances of similar shape that can combine to these receptors such as endogenous opiates that bind to opiates receptors, adrenaline and noradrenaline that combine to adrenoceptors.

II. Mechanisms of drug binding to receptors:

1. Covalent binding : are strong and usually irreversible bonds and rarely mediate drug effect as cytotoxic drugs.
2. Electrostatic bonds: are more common than covalent binding.
3. Hydrophobic bonds: are usually weak bonds and are important in highly lipid soluble drugs binding with the lipids cell membranes.

Receptors can be divided into three different types:

1. Receptors linked to ion channels: these receptors regulate the flow of ions across their channels in the cell membrane example; nicotinic cholinergic receptors and Na^+ ion channels, GABA receptors and Cl^- ion channels. They are activated in milliseconds.
2. G-protein coupled receptors: these receptors are linked to G protein which mediates the intracellular action by binding to guanosine triphosphate. This will lead to the activation of a second messenger mechanism called adenylcyclase which results in the production of cyclic-adenosine

monophosphate(cAMP), and this regulates protein phosphorylation. They act in seconds to minutes, as the beta-adrenoceptors.

3. Intracellular receptors; these receptors are located inside the cell and therefore the drug molecule must diffuse to the inside of the cell to interact with these receptors as in estrogen receptors which are located in the nucleus of the cell and they stimulate DNA and proteins synthesis and usually take hours to act, also corticosteroids have similar receptors

III. Second messenger : The second messenger is an intracellular component that can transmit the effect of the drug to the inside of the cell following receptor stimulation, such as cyclic adenosine monophosphate (c-AMP) and calcium ions, changes in this second messenger will produce the drug effects as muscle contraction or relaxation or gland secretion.

A. Receptors regulations: The response to drug depends on the number of receptors occupied. The number of receptors may be affected by the continued presence of the drug. In general, the number of receptors declines with continuous agonist drug administration and this will lead to decrease in drug response (receptors down-regulation) this is in order to protect the cell from excessive stimulation. The reduction in receptors occurs by the process of endocytosis, which means that the cell engulfs the receptors and degrades it.

B. Tachyphylaxis: rapid reduction in the response to the drug following repeated administration (this is due to receptors down-regulation). Continuous administration of the antagonist will increase the number of receptors (receptors up-regulation), which makes sudden withdrawal of the antagonist dangerous after prolonged use as beta-blockers

C. Dose response relation

The effect produced by a drug is generally a function of the amount of the drug administered "dose-Response Curve". The magnitude of the drug effect depends on its concentration at the receptor site, which is in term determined by the dose of the drug administered and affected by factors related to the drug characteristics and the pharmacokinetics parameters.

D. Dose-Response Curve:

As the concentration of the drug increases, the magnitude of its pharmacological effect will also increase (i.e. increasing the drug amount will increase the response). The curve has S shape with a linear part in the middle.

a. Quantal-dose response (dose percent effect): for determination of drug response in the population, it is used for all or none effect as prevention of convulsion, cardiac arrhythmias and in acute toxicity studies.

Therapeutic index is the ratio of toxic dose to the effective dose

Therapeutic index = toxic dose / effective dose

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

Lethal dose (LD50): it is the dose that kills 50% of the experimental animals; it is also useful in finding the therapeutic dose in the early experimental studies of drug discovery. It can also be used to measure the therapeutic index a follow:

Therapeutic index = LD50/ ED50

LD 50 is the lethal dose in 50% of animals

ED50 is the effective dose in 50% of the animals

b. Agonist: any substance which has the affinity to combine with the receptors and causes receptors stimulation and pharmacological action. Example is acetylcholine which combines to muscarinic receptors and adrenaline which combines to the adrenergic receptors.
c. Partial agonist: is a drug which has affinity and some efficacy to the receptors and it does not produce maximum effect even when all the receptors are occupied and it may antagonize the action of other agonists that have a greater efficacy.
d. Antagonist: is the substance which has the affinity for the receptors but when combines with the receptors does not cause stimulation. The antagonist usually blocks or antagonizes the effect of the agonist. Example, atropine which can combine with muscarinic receptors and antagonize the effects of acetylcholine, also propranolol can combine with adrenergic receptors and antagonized the effects of adrenaline
e. Sensitivity: is the ability of a given dose of a drug to act on one system rather than the other.
f. Affinity : is the ability to combine with receptors , drugs with high affinity will displace drugs with low affinity from receptors binding
g. Potency: is a given response for certain receptor occupation, the more potent drug will give similar response at lower doses than the less potent drug, this usually determines the dose of the drug
h. Efficacy: is the maximum response to drug, this means no further increase in response occurs when we increase the dose. Drugs can have high efficacy as furosemide or low efficacy as spironolactone

i. Competitive antagonism : when two drugs compete on the same receptor site, it occurs between two drugs of similar chemical structure and usually occurs between the agonist and its antagonist on the same receptor site, example atropine can compete with acetylcholine on the muscarinic receptors. The antagonist causes parallel shift to the right of the dose response curve (i.e. you need higher dose to produce the same effect).

j. Physiological antagonism: Occurs when two drugs antagonize the effect of each other, but they act on two different receptors (the drugs have opposing pharmacological actions). Example is histamine which acts on histaminic receptors and causes vasodilatation, while adrenaline acts on adrenergic receptors and causes vasoconstriction , so adrenaline is a physiological antagonist to histamine and it is useful in anaphylactic reactions

Factors modifying drug response:

1. Age: various physiological changes with age that might affect the pharmacokinetics or pharmacodynamics of drugs include body fat contents, volume of distribution, hepatic blood flow, glomerular filtration rate and changes in homeostatic mechanisms.
2. Body weight: as this affects the body fluids and fat, which may change the drug concentration in the body.
3. Gender: generally lower doses for females also note hormonal, changes, menstruation, pregnancy and lactation. This can also modify the adverse effects of the drugs.

4. Racial factors Negros, Asians and Caucasians, may show different response to the same drug.
5. Genetic factors: as variation in cytochrome P450 enzymes will alter the rate of drug metabolism, also genetic deficiency of G6PD enzyme will lead to hemolysis of the red blood cell by some drugs as primaquine.
6. Disease states: include hepatic and renal diseases. These can change drug metabolism rate, drug clearance from the body and the body response to drugs.
7. Drug: dose, route of administration, frequency of administration, drug interactions, tolerance and tachyphylaxis.

- No drug only produces a single specific effect
- Drug may act on the same receptors at different cells or it may act on different receptors at the same time
- Drug effects can be divided into toxic (adverse or unwanted) and (therapeutic or useful)