Pharmacodynamics

Mechanisms of Drug Action

Receptors

Receptors are macromolecular which are protein or lipoprotein in nature situated on the cell membrane or within the cell with which the drugs binds mostly reversibly or irreversibly and form a drug receptor complex.

Classification of receptors:

According to their location,

a. **On the cell membrane / Membrane receptor,** e.g. Adrenoceptors (α and β), cholinergic receptors, all peptide hormone receptors (insulin receptor).

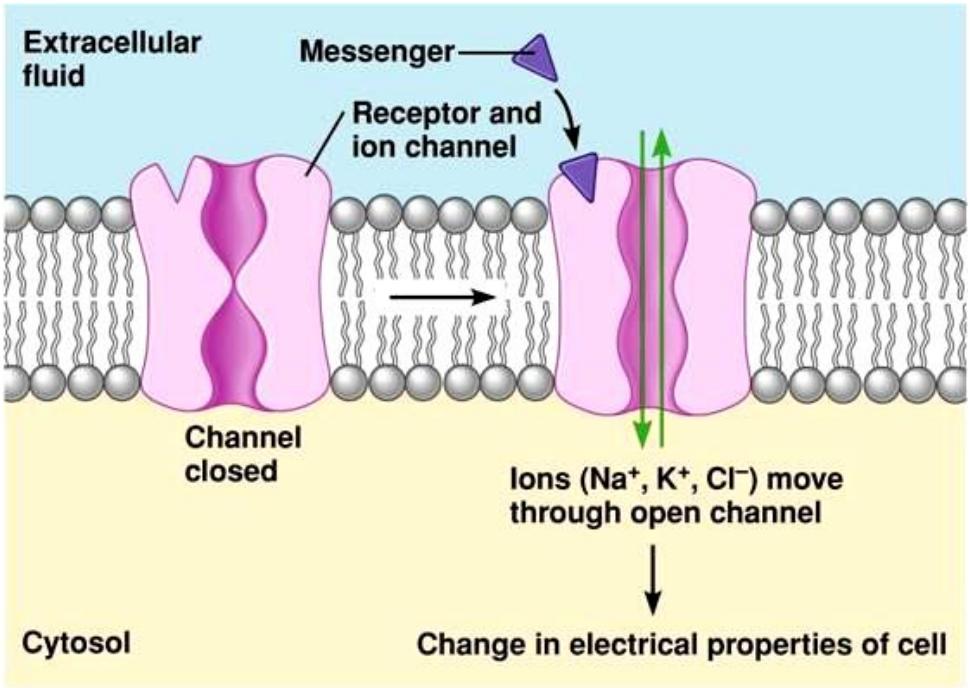
b. **Within cytoplasm / Cytoplasmic receptors,** e.g. steroid hormone receptors.

c. **Within nucleus / Nuclear receptors,** e.g. thyroid hormone receptors.

According to molecular structure and transduction mechanism-

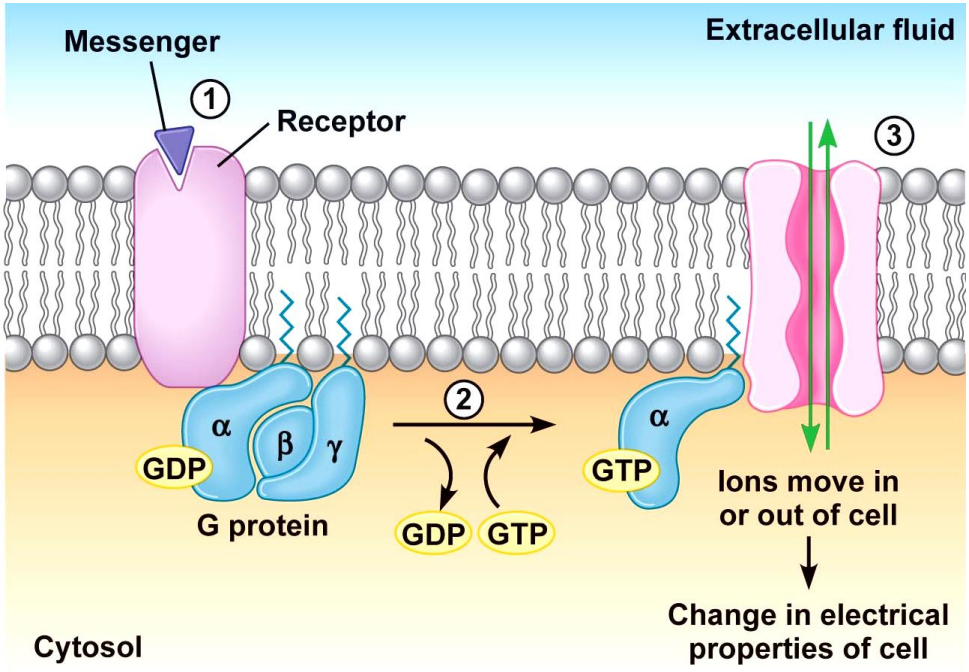
Type 1: Ion channel receptors / Receptors with ion channel (fast receptor)

Here, agonist binding to the receptor causes opening of ion channels (Na^+, K^+, Ca^{2+},or Cl^- channel) resulting in hyperpolarisation or depolarisation. These channels are coupled to cell surface receptors. E.g. GABA receptor etc.



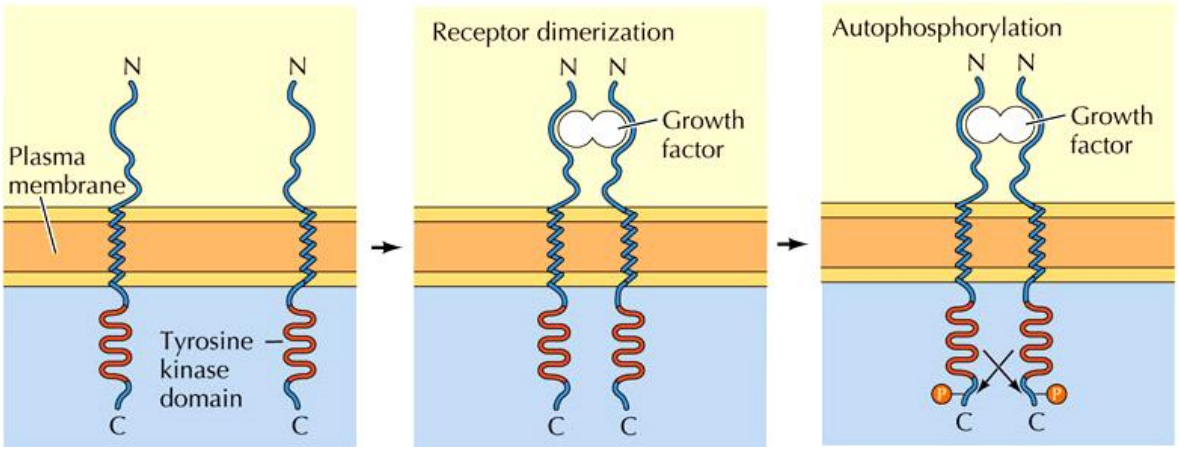
Type 2: G-protein coupled receptors (slow receptor)

Agonist binding to the receptor triggers the activation of a G-protein (GTP activated protein). Then the G-protein causes stimulation of an effector enzyme resulting in the formation of second messenger which gives desired effects. E.g. Adrenoceptors (α and β), dopamine receptors, 5-HT (5-Hydroxy tryptamine) receptors, opioid receptors etc.



Type 3: Kinase linked receptor / Enzymatic receptors

Here, the receptors have an extracellular ligand binding domain and an intracellular enzyme domain which may be a protein tyrosine kinase, a serine kinase or a guanylyl cyclase. Ligand binding to the extracellular domain stimulates the enzymatic activity of the intracellular domain. e.g, insulin receptors, various growth factor receptors.



Type 4: Intracellular receptors

Here, receptors are intracellular (cytoplasmic or nuclear) soluble proteins which respond to lipid soluble chemical messengers that penetrate the cell.

E.g. Steroid receptors, thyroid receptors, receptors for vitamin A etc.

Some important definitions

Ion channels

Biological membranes contain several specific pores through which ions such as Na^+, K^+, Ca^{2+} or Cl^- etc. move. These channels are termed as Na^+ channel, K^+channel, Ca^{2+}channel, Cl^- channel respectively.

First messenger

The chemicals which directly act on the receptor.

E.g.: Drug

Neurotransmitters

Hormones

Autacoids

Second messenger

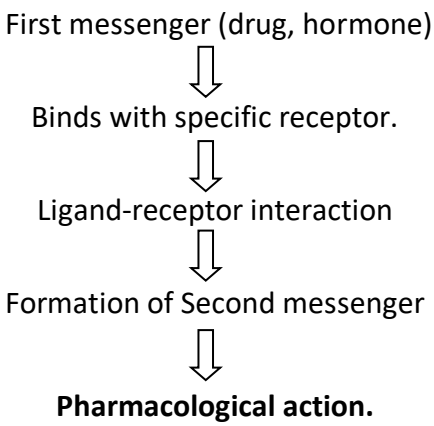
When first messenger binds with its specific receptor, the ligand-receptor complex is formed which subsequently causes synthesis and release of another intracellular regulatory molecule known as second messenger.

E.g.: c AMP (cyclic adenosine monophosphate)

c GMP (cyclic guanosine monophosphate)

DAG (Diacylglycerol)

IP_3 (Inositol triphosphate)



Affinity

It is the tendency of a drug to combine with receptor.

Efficacy or Intrinsic activity

The ability / capacity of a drug to bind with the receptor and produce pharmacological response.

Agonist

Drug which has both affinity for receptor and efficacy is called agonist.

Example- salbutamol is a β-receptor agonist. It causes relaxation of the bronchial smooth muscle by activating β_2-receptor of bronchial smooth muscle.

Antagonist

Drug that has the same affinity as the agonist for the receptor but lacks efficacy i.e. not capable of eliciting a pharmacological action. In other words, an antagonist is the drug that interferes with the biding of the agonist with its receptor but does not have any effect of its own. E.g. Propranolol is a β-receptor antagonist.

Mechanisms of drug action

1. **By physical means:**

   A physical property is responsible for its action. For example, Osmotic diuretic such as mannitol acts by osmosis; activated charcoal adsorb alkaloid poisons.

2. **By direct chemical action:**

   Drugs act through direct chemical reactions, e.g. antacids neutralize gastric HCl.

3. **Through enzymes:**

   Enzymes are very important targets of drug action. Drugs are either increase or decrease the rate of enzymatically mediated reactions.

   Methotrexate, used as an anticancer drug, is an inhibitor of dihydrofolate reductase.

4. **Through receptors/ receptor mechanism of drug action:**

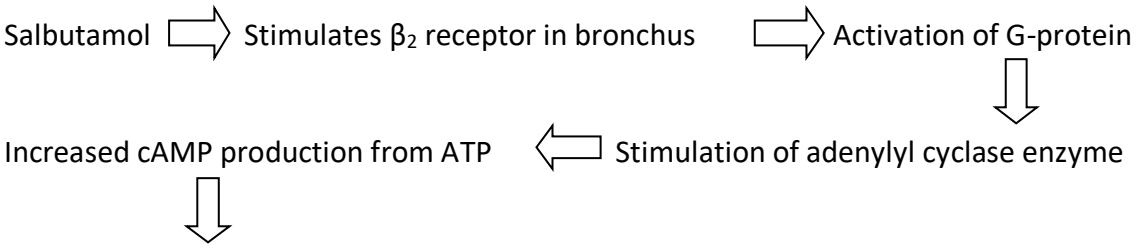
   When a drug is administered, it binds to its specific receptors and form drug-receptor complex. This complex acts by the following ways:

A. Direct control of ion channels

Here, agonist binding to the receptor causes opening of ion channels (Na^+, K^+, Ca^{2+}, or Cl^- channel) resulting in hyperpolarization or depolarization. These channels are coupled to cell surface receptors. E.g. Nicotinic acetylcholine receptor, GABA receptor etc. Acetylcholine binding to the nicotinic acetylcholine receptor causes in the opening of Na^+ channel resulting in depolarization. As a result, muscle contraction occurs.

B. Control of G-protein and formation of second messenger

Agonist binding to the receptor triggers the activation of a G-protein (GTP activated protein). Then the G-protein causes stimulation of an effector enzyme resulting in the formation of second messenger which gives desired effects. E.g. Adrenoceptors (α and β), muscarinic acetylcholine receptors, dopamine receptors, 5-HT (5-Hydroxy tryptamine) receptors, opioid receptors etc.



Bronchodilatation (Relaxation of bronchial muscle)

C. Direct control of effector enzyme:

Here, the receptors have an extracellular ligand binding domain and an intracellular enzyme domain which may be a protein tyrosine kinase, a serine kinase or a guanylyl cyclase. Ligand binding to the extracellular domain stimulates the enzymatic activity of the intracellular domain. e.g, insulin receptors, various growth factor receptors.

Insulin receptor is glycoprotein complex consisting of two α and β subunits linked by disulphide bridges. α – subunits are extracellular and β subunits are transmembrane proteins that contain a tyrosine kinase. Insulin binding to the α-subunits causes activation of β subunit tyrosine kinase activity which initiates activation of cascade of key enzymes and causes phosphorylation and dephosphorylation giving specific response.

D. Control of DNA transcription:

Here, receptors are intracellular (cytoplasmic or nuclear) soluble proteins which respond to lipid soluble chemical messengers that penetrate the cell. E.g. Steroid receptors, thyroid receptors.

Mechanism of steroid action is given below:

Steroid Hormone (Drug)

⇩

Penetrates the cell membrane and binds to cytoplasmic receptor forming steroid-receptor (SR complex) complex.

⇩

SR complex enters into the nucleus

⇩

Formation of m RNA by transcription process

⇩

Formation of new proteins from m RNA by translation process.

⇩

Modification of cellular function (metabolic action, anti-inflammatory action etc.)

Dose-response relationship

The relationship between the dose and the response or pharmaceutical effects is known as dose-response relationship. The curve showing dose-response relationship is known as dose-response relationship curve. In this type of curve, dose is plotted on the horizontal axis and response is plotted on the vertical axis.

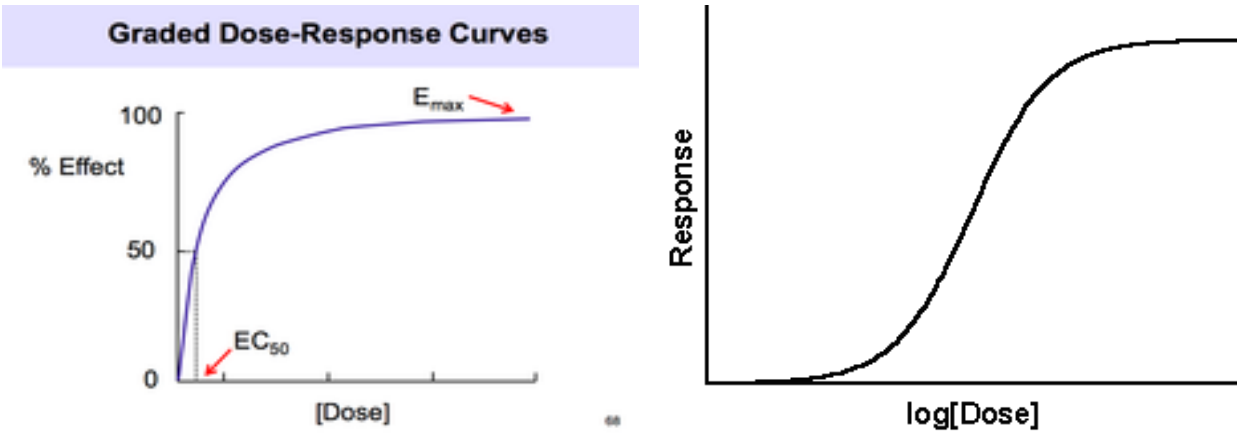
There are two types of dose-response relationship curve,-such as,

1. Graded dose-response curve or log dose response curve

Gradation of response in relation to gradation of dose is called graded dose-response curve. The curve shows that increased dose will increase response in a graded fashion up to a certain limit. When all the receptors are occupied, further increased dose will not increase response.

- ✓ If dose is plotted on the horizontal axis and response is plotted on the vertical axis, the curve will be rectangular hyperbola.
- ✓ If log dose is plotted on the horizontal axis and response is plotted on the vertical axis, the curve will be S-shaped or sigmoid.

Graded dose-response curve is helpful to find out the lowest concentration of drug that produces maximal effect.



2. Quantal dose-response curve / Arrythmatic dose response

Quantal dose-response curves determine the dose of a drug required to produce a specified magnitude of effect (e.g., relief of headache) in a large number of individual patients or experimental animals.

For example, the dose at which 50% of individuals exhibit the specified quantal effect is called median effective dose (ED_{50}). If the ED_{50} of two drugs for producing a specified quantal effect are 5 and 500 mg respectively, the first drug is 100 times potent than the second one for that particular effect.

Drug Combination

Purpose of combination therapy:

- ➔ To obtain a desired therapeutic effect,
- ➔ To treat co-existing diseases,
- ➔ To broaden the spectrum in case of antibiotic therapy,
- ➔ To delay the emergence of malignant cells in cancer chemotherapy,
- ➔ To resist the development of microbial resistance to antibiotics,
- ➔ To minimize the adverse drug reaction.

Combined effects of drugs

When two or more drugs are given simultaneously or in quick succession, they may produce-

- ✓ Synergism or
- ✓ Antagonism

Drug synergism:

When the net effects of two drugs consumed together are equal or are greater than the sum of the effects of individual drug. It is called drug synergism.

Effect of drug (A+B) > Effect of drug A+ Effect of drug B

It is of two types-

1. Summation or additive effect

When the net effect of two drugs used together is equal to the sum of the individual drug effects, the drugs are said to have an additive effect.

Effect of drug (A+B) = Effect of drug A+ Effect of drug B.

For example, the combination of thiazide diuretic and a Beta blocker (beta adrenergic blocking drug) is used for the treatment of hypertension.

Another example is the combination of Aluminium hydroxide and magnesium trisillicate used for the treatment of peptic ulcer.

2. Potentiation:

When the net effect of two drugs used together is greater than the sum of the individual drug effects, the drugs are said to have potentiation effect.

As an example, Promethazine hydrochloride, an antihistamine, when given with a painkilling narcotic such as Meperidine intensifies its effect, thereby cutting down on the amount of the narcotic needed.

2. Drug antagonism

The effects of one drug can be reduced or abolished by the presence of another drug. This is called drug antagonism. It is of three types, such as,-

- ✓ **Chemical,**
- ✓ **Physiological and**
- ✓ **Pharmacological antagonism.**

Chemical antagonism

When a drug antagonizes the effect of another drug by simple chemical reaction without acting on the receptor. For example, antacid neutralizes the gastric acid.

Physiological antagonism

When the physiological effect of a drug is antagonized by another drug by acting on two different types of receptors. For example, acetylcholine causes constriction whereas adrenaline causes dilatation of pupil. Noradrenaline contracts vascular smooth muscle to increase blood pressure, whereas histamine relaxes vascular smooth muscle to decrease blood pressure.

Pharmacological antagonism

When a drug antagonizes the effect of another drug by acting on the same receptor, it is called Pharmacological antagonism. It is of two types-

I. Competitive antagonism

In this case, both the agonist and antagonist compete for the same receptor and are able to displace each other at the same recognition site on the receptor. For example, Propranolol (antagonist of β_2-receptor of bronchus) antagonizes the effect of salbutamol (agonist of β_2-receptor of bronchus→ Bronchodilation)

II. Non competitive antagonism

The term "non-competitive antagonism" can be used to describe two distinct phenomena: one in which the antagonist binds to the active site of the receptor, and one in which the antagonist binds to an **allosteric site** of the receptor. A **non-competitive antagonist** inhibits the response by binding to an area separate to the active site of the receptor. For example, Diazepam is a non-competitive antagonist of bicuculline.