Introduction to pharmacology

Dr.Iman **Lec:1**

Pharmacology: study of the effects of chemical substances on the function of living systems.

Clinical pharmacology: all aspects of the scientific study of the drug in man

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Objectives:

- General aspects of rational, safe and effective drug therapy.
- Drug therapy of individual disease.
- Introduction of new medicines

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Drug:

Chemical substance used in diagnosis, cure, prevention, control of various disease state, alleviate symptoms.

The goal of drug therapy is to:

- Cure disease → antibiotics in treatment of bacterial infection.
- Alleviate symptoms → antacid in treatment of dyspepsia.
- Prevention → vaccination.
- Control disease state, e.g. Rx of diabetes or hypertension
- Replace deficiencies → hormones, vitamins.

Drug – body – interactions:

Pharmacodynamic → the effect of drug on the body.

Pharmacokinetic → the effect of body on drugs.

Pharmacodynamics

- Most drugs act by altering the body's control system, which include local hormones, receptors, enzymes, chemotransmitters, ... by the following mechanisms:

Mechanisms of drug actions:

On the cell membrane:

Action on specific receptors e.g. agonist and antagonist on adrenoceptors, histamine receptors.

Interference with passage of ions across cell membrane e.g. Ca^{+2}-channel blockers.

Inhibition of membrane – bound enzymes e.g.→ digoxin inhibit membrane ATP-ase enzyme in cardiac muscle.

On metabolic process within the cell:

Enzymatic inhibition e.g. aspirin inhibits cyclo-oxygenase enzyme.

- Inhibition of transport process across the cells e.g. probenecid blocks anion transport in renal tubular cells → ↓ excretion of penicillin, ↑ excretion of urate.
- Incorporation into larger molecules e.g. anticancer drugs incorporate into m-RNA.
- Altering metabolic processes unique to microorganisms e.g. penicillin inhibit bacterial cell wall synthesis.

III. Outside the cell:

- Direct chemical interaction e.g. antacids.
- Osmosis e.g. purgatives ($MgSO_4$), diuretics → mannitol.

Receptors

specialized target protein macromolecules present on cell surface or intracellular, bind with a drug → change of biological events → drug response,or a protein that transducing extracellular signal into intracellular response**. or** a receptor is any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes, nucleic acids, and structural proteins can be considered to be pharmacologic receptors.

Receptor + drug (agonist) → alteration of receptor confirmation → intracellular changes → effect, e.g. adrenaline (^{1st} messenger) + β receptor → ↑ activity of adenylyl cyclase → ↑ cAMP (^{2nd} messenger) → response: (either beneficial, or harmful → adverse effects).

The magnitude of the response is proportional to the number of drug – receptor complexes.

Nature of receptors:

. Regulatory proteins → mediate action of endogenous signals e.g. neurotransmitters and hormones.
. Enzymes: e.g. dihydrofolatereductase (receptor for methotrexate).
. Transport proteins: e.g. Na^+ - K^+ - ATP-ase (receptor for digitalis).
. Structural proteins: e.g. tubulin receptor for colchicin.

Drug – receptor binding forces:

. Most commonly electrostatic and hydrogen bonds, as well as Vander Waals forces, **these are weak bonds → reversible binding.**
. Strong forces: e.g. covalent bonds → **irreversible binding.**

The size, shape and charge distribution of the drug determines which sites in the cells and tissues of patient can interact with drug i.e. determine the selectivity of receptors.

Families of the receptors

- **Channel linked receptor (Ionotropic receptor) or transmembrane ligand- gated ion channels:**

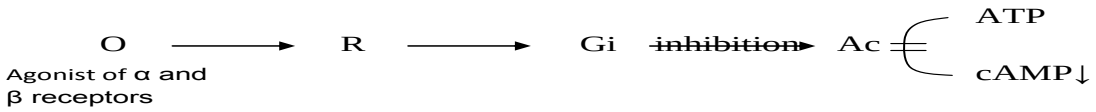
*Receptor coupled to membrane ion channel, ↑ permeability to a particular ion, peak action within fraction of millisecond, and terminates within few milliseconds.e.g nicotinic &GABA receptors, Stimulation of nicotinic receptors by ACH →sodium influx &generation of action potential →M .contraction. **Benzodiazepines** enhance the stimulation of GABA receptors by GABA →increased chloride influx & hyperpolarization of the respective cell.

2-GPCR(G-protein coupled receptors)

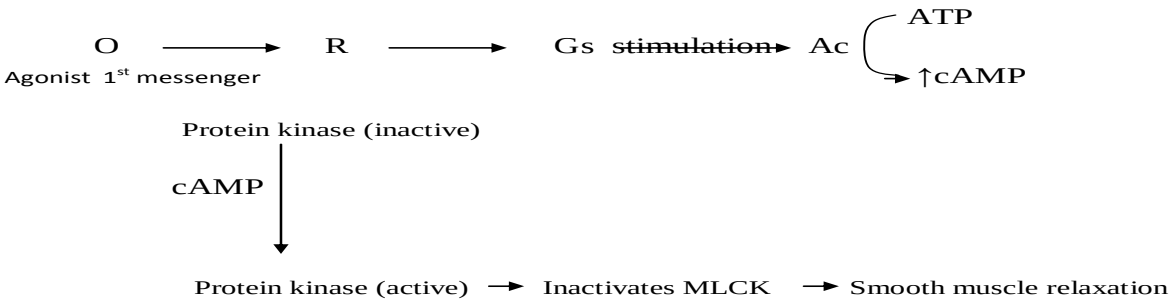
Receptors are consist of a single peptide that has seven membrane –spanning regions,& coupled to G-protein, which is a membrane protein comprising three subunits (α binds toGTP, β, γ), 3 main classes of G-protein include Gs, Gi and Gq. the effect lasted several second → minutes. Targets for G-proteins include**:**

. **cAMP (second messenger system):**

Gi: inhibits adenylatecyclase enzyme leading to ↓ C-AMP concentration e.g**. morphine – opioid receptor and some muscarinic – Ach receptors of the cardiac muscle.**

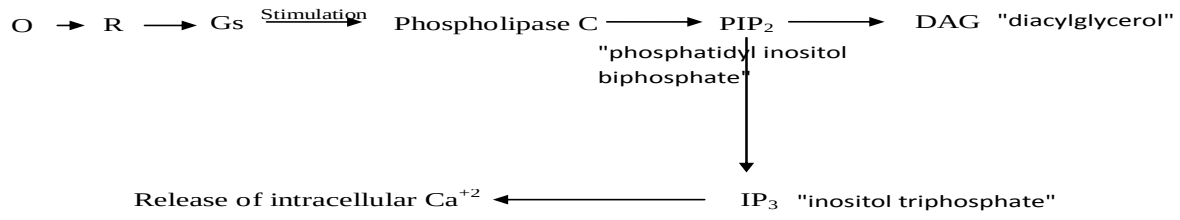


Gs:in smooth muscle stimulates adenylatecyclase enzyme → to ↑ cAMP concentration which stimulates protein kinase enzyme leading to inactivation of **MLCK** (myosin light chain kinase) and smooth muscle relaxation.



A- Phospholipase C/inositol (2nd messenger system):

e.g. α-adrenoceptor agonists on smooth muscle.



3. Enzyme linked membrane bound receptor:
Protein kinase is incorporated within the receptor e.g. release of inflammatory mediators and insulin(lasts minutes----hours).
4-Intracellular receptors: e.g. steroids in cytoplasm and thyroid hormone act on nuclear receptors, stimulate gene transcription leading to protein synthesis, the response takes hours or days to occur.

Characteristics of receptors

Receptors do not remain constant in number. -
1-Desensitization includes down regulation&tachyphylaxis
Continues exposure to agonist lead to ↓ in number of receptors (down regulation), &results in molecular changes in membrane- bound receptors ,such as the receptors undergo endocytosis e.g. morphine on opioid receptors.
-Prolong contact with antagonist → up regulation and formation of new receptors e.g. β-ockers on cardiac β-adrenergic receptors.
3-Spare receptors
A full response can occur when only a small fraction of receptors is occupied, often less than 1%.. This system is said to have spare receptors or receptor reserve.

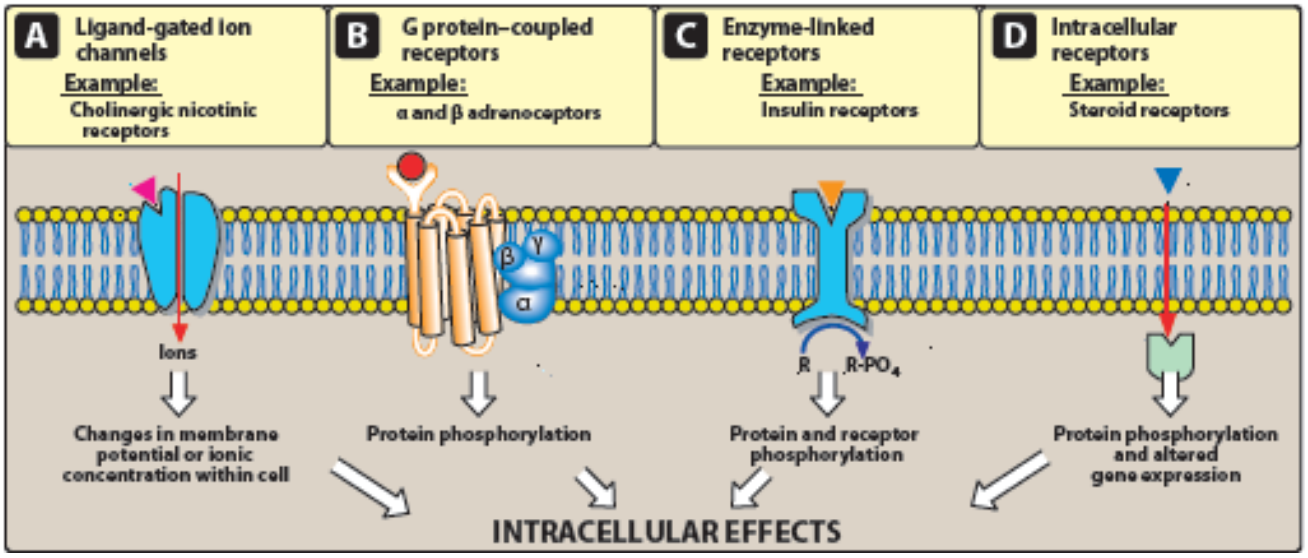
E.g. receptors respond to hormones, neurotransmitters and peptide → can amplify signal duration and intensity so, acceptable biological response can be achieved with lower concentration of hormone (e.g. insulin) than would be the case if fewer receptors were provided.
Economy of hormone or transmitter is achieved at the expense of providing more receptors.
In the heart, only 5-10% are spared**.**

Agonist :drugs that are recognized by the receptor, occupy it and activate it to produce a response e.g. drugs that resemble natural transmitters but resist degradations and act for longer time **e.g. salbutamol – β-agonist.**
Antagonist (blocker): drugs that are recognized by the receptor, occupy it without activating a response, thereby preventing natural agonist from exerting its effect **e.g. propranolol β-adrenoceptor blocker.**
Partial agonist:1- drugs which occupy the receptor and capable of a low degree of activation **e.g. pindolol – β – partial agonist.**
2-is a drug with higher affinity and & lower efficacy than full agonist, it has both agonist and antagonist actions, if it is used alone it acts as low **efficacy agonist** and produce a lower response than the full agonist. But it acts as antagonist when used in presence of

a full agonist, because of its high affinity to the receptors and reduces the occupancy of receptors by full agonist so ↓ its action.

e.g.

- Nalorphine is a partial agonist that acts like morphine, when used alone produce analgesia, sedation and respiratory depression, but when used before morphine (in rabbits) it antagonized morphine action.
- Pindolol (antagonist of catecholamines) which is β-blocker that produces less reduction in heart rate than other β-blockers because of its partial agonist activity (or intrinsic sympathomimetic effect).



Drug	Affinity	Efficacy
Agonist	↑	↑
Antagonist	↑	- (zero)
Partial agonist	↑↑	↓ (low)
Inverse agonist	↑	↑