Faculty of Pharmaceutical Sciences

Rama University Kanpur (U.P)

BP-404 T PHARMACOLOGY- 1(Theory)
B.PHARM 4th SEM.

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UNIT-II (PART I) 06 Hours

General Pharmacology

Pharmacodynamics- Principles and mechanisms of drug action. Receptor theories and classification of receptors, regulation of receptors. drug receptors interactions signal transduction mechanisms, G-protein–coupled receptors, ion channel receptor, transmembrane enzyme linked receptors, transmembrane JAK-STAT binding receptor and receptors that regulate transcription factors,

PRINCIPLES OF DRUG ACTION

Drugs (except those gene based) do not impart new functions to any system, organ or cell; they only alter the pace of ongoing activity. However, this alone can have profound medicinal as well as toxicological impact.

The basic types of drug action can be broadly classed as:

1. Stimulation It refers to selective enhancement of the level of activity of specialized cells, e.g. adrenaline stimulates heart, pilocarpine stimulates salivary glands. However, excessive stimulation is often followed by depression of that function, e.g. high dose of picrotoxin, a central nervous system (CNS) stimulant, produces convulsions followed by coma and respiratory depression.

2. Depression It means selective diminution of activity of specialized cells, e.g. barbiturates depress CNS, quinidine depresses heart, omeprazole depresses gastric acid secretion. Certain drugs stimulate one type of cells but depress the other, e.g. acetylcholine stimulates intestinal smooth muscle but depresses SA node in heart. Thus, most drugs cannot be simply classed as stimulants or depressants.

3. Irritation This connotes a nonselective, often noxious effect and is particularly applied to less specialized cells (epithelium, connective tissue). Strong irritation results in inflammation, corrosion, necrosis and morphological damage. This may result in diminution or loss of function.

4. Replacement This refers to the use of natural metabolites, hormones or their congeners in deficiency states, e.g. levodopa in parkinsonism, insulin in diabetes mellitus, iron in anaemia.

5. Cytotoxic action Selective cytotoxic action on invading parasites or cancer cells, attenuating them without significantly affecting the host cells is utilized for cure palliation of infections and neoplasms, e.g. penicillin, chloroquine, zidovudine, cyclophosphamide, etc.

MECHANISM OF DRUG ACTION

Only a handful of drugs act by virtue of their simple physical or chemical property; examples are:

• Bulk laxatives (ispaghula)—physical mass

• Dimethicone, petroleum jelly—physical form, opacity

• Paraamino benzoic acid—absorption of UV rays

• Activated charcoal—adsorptive property

• Mannitol, mag. sulfate—osmotic activity

Majority of drugs produce their effects by interacting with a discrete target biomolecule, which usually is a protein. Such mechanism confers selectivity of action to the drug. Functional proteins that are targets of drug action can be grouped into four major categories, viz.

Enzymes,

Ion Channels,

Transporters And

Receptors

ENZYMES- Almost all biological reactions are carried out under catalytic influence of enzymes; hence, enzymes are a very important target of drug action. Drugs can either increase or decrease the rate of enzymatically mediated reactions. However, in physiological systems enzyme activities are often optimally set. Thus, stimulation of enzymes by drugs, that are truly foreign substances, is unusual.

Enzyme stimulation is relevant to some natural metabolites only, e.g. pyridoxine acts as a cofactor and increases decarboxylase activity.

Enzyme inhibition

Some chemicals (heavy metal salts, strong acids and alkalies, formaldehyde, phenol, etc.) denature proteins and inhibit all enzymes nonselectively. They have limited medicinal value restricted to external application only.

competitive or noncompetitive enzyme inhibition.

(i) **Competitive (equilibrium type)** The drug being structurally similar competes with the normal substrate for the catalytic binding site of the enzyme so that the product is not formed or a nonfunctional product is formed (Fig. 4.1A), and a new equilibrium is achieved in the presence of the drug. Such inhibitors increase the kM but the Vmax remains unchanged.

(ii) **Noncompetitive** The inhibitor reacts with an adjacent site and not with the catalytic site, but alters the enzyme in such a way that it loses its catalytic property. Thus, kM is unchanged but Vmax is reduced.

ION CHANNELS- Proteins which act as ion selective channels participate in transmembrane signaling and regulate intracellular ionic composition. This makes them a common target of drug action Drugs can affect ion channels, some of which actually are receptors, because they are operated by specific signal molecules either directly and are called ligand gated channels (e.g. nicotinic receptor) or through G-proteins and are termed G-protein regulated channels (e.g. cardiac β1 adrenergic receptor activated Ca2+ channel). Drugs can also act on voltage operated and stretch sensitive channels by directly binding to the channel and affecting ion movement through it.

TRANSPORTERS Several substrates are translocated across membranes by binding to specific transporters (carriers) which either facilitate diffusion in the direction of the concentration gradient or pump the metabolite/ion against the concentration gradient using metabolic energy. Many drugs produce their action by directly interacting with the solute carrier (SLC) class of transporter proteins to inhibit the ongoing physiological transport of the metabolite/ion.

RECEPTOR: It is defined as a macromolecule or binding site located on the surface or inside the effector cell that serves to recognize the signal molecule/drug and initiate the response to it, but itself has no other function.

The following terms are used in describing drug-receptor interaction:

Agonist An agent which activates a receptor to produce an effect similar to that of the physiological signal molecule.

Inverse agonist An agent which activates a receptor to produce an effect in the opposite direction to that of the agonist.

Antagonist An agent which prevents the action of an agonist on a receptor or the subsequent response, but does not have any effect of its own.

Partial agonist An agent which activates a receptor to produce submaximal effect but antagonizes the action of a full agonist.

Ligand (Latin: ligare—to bind) Any molecule which attaches selectively to particular receptors or sites. The term only indicates affinity or ability to bind without regard to functional change: agonists and competitive antagonists are both ligands of the same receptor.

Nature of receptors Receptors are regulatory macromolecules, mostly proteins, though nucleic acids may also serve as receptors. Hundreds of receptor proteins have been isolated, purified, cloned and their primary amino acid (AA) sequence has been worked out. Molecular cloning has also helped in obtaining the receptor protein in larger quantity to study its structure and properties, and in subclassifying receptors.

Receptor subtypes

Even at an early stage of evolution of receptor pharmacology, it was observed that actions of acetylcholine could be grouped into 'muscarinic' and 'nicotinic' depending upon whether they were mimicked by the then known alkaloids muscarine or nicotine. Accordingly, they were said to be mediated by two types of cholinergic receptors, viz. muscarinic (M) or nicotinic (N)

Ahlquist (1948) divided adrenergic receptors into 'α' and 'β' on the basis of two distinct rankorder of potencies of adrenergic agonists

These receptors have now been further subdivided

(M1, M2 ….M5),

(NM, NN)

(α1, α2) (β1, β2, β3)

Action-Effect Sequenc

Drug action It is the initial combination of the drug with its receptor resulting in a conformational change in the latter (in case of agonists), or prevention of conformational change through exclusion of the agonist (in case of antagonists).

Drug effect It is the ultimate change in biological function brought about as a consequen of drug action, through a series of intermediate steps.

TRANSDUCER MECHANISMS Considerable progress has been made in the understanding of transducer mechanisms which in most instances have been found to be highly complex multistep processes that provide for amplification and integration of concurrently received extra- and intra-cellular signals at each step. The transducer mechanisms can be grouped into 5 major categories. Receptors falling in one category also possess considerable structural homology, and belong to one super-family of receptors.

1. **G-protein coupled receptors (GPCRs)** These are a large family of cell membrane receptors which are linked to the effector (enzyme/ channel/carrier protein) through one or more GTPactivated proteins (G-proteins) for response effectuation. All such receptors have a common pattern of structural organization.
   A number of G proteins distinguished by their α subunits have been described-
   Gs : Adenylyl cyclase activation, Ca2+ channel opening
   Gi : Adenylyl cyclase inhibition, K+ channel opening
   Go : Ca2+ channel inhibition
   Gq : Phospholipase C activation

There are three major effector pathways through which GPCRs function.

(a) Adenylyl cyclase: cAMP pathway Activation of AC results in intracellular accumulation of second messenger cAMP which functions mainly through cAMP-dependent protein kinase (PKA). The PKA phosphorylates and alters the function of many enzymes, ion channels, transporters, transcription factors and structural proteins to manifest as increased contractility/impulse generation (heart), relaxation (smooth muscle), glycogenolysis, lipolysis, inhibition of secretion/mediator release, modulation of junctional transmission, hormone synthesis, etc.

(b) Phospholipase C: IP3-DAG pathway Activation of phospholipase Cβ (PLcβ) by the activated GTP carrying α subunit of Gq hydrolyses the membrane phospholipid phosphatidyl inositol 4,5-bisphosphate (PIP2) to generate the second messengers inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). The IP3 being water soluble diffuses to the cytosol and mobilizes Ca2+ from endoplasmic reticular depots.

(c) Channel regulation The activated Gproteins (Gs, Gi, Go) can also open or inhibit ionic channels specific for Ca2+ and K+, without the intervention of any second messenger like cAMP or IP3, and bring about hyperpolarization/ depolarization/changes in intracellular Ca2+. The Gs opens Ca2+ channels in myocardium and skeletal muscles, while Gi and Go open K+ channels in heart and smooth muscle as well as inhibit neuronal Ca2+ channel.

2. Ion channel receptor These cell surface receptors, also called ligand gated ion channels, enclose ion selective channels (for Na+, K+, Ca2+ or Cl^{-}) within their molecules. Agonist binding opens the channel and causes depolarization/hyperpolarization/ changes in cytosolic ionic composition, depending on the ion that flows through. The nicotinic cholinergic, GABAA, glycine (inhibitory AA), excitatory AA-glutamate (kainate, NMDA and AMPA) and 5HT3 receptors fall in this category.

3. Transmembrane enzyme-linked receptors This class of receptors are utilized primarily by peptide hormones, and are made up of a large extracellular ligand binding domain connected through a single transmembrane helical peptide chain to an intracellular subunit having enzymatic property.

4. Transmembrane JAK-STAT binding receptors These receptors differ from RTKs in not having any intrinsic catalytic domain. Agonist induced dimerization alters the intracellular domain conformation to increase its affinity for a cytosolic tyrosine protein kinase JAK (Janus Kinase). On binding, JAK gets activated and phosphorylates tyrosine residues of the receptor, which now bind another free moving protein STAT (signal transducer and activator of transcription).

5. Receptors regulating gene expression (Transcription factors, Nuclear receptors) In contrast to the above 3 classes of receptors, these are intracellular (cytoplasmic or nuclear) soluble proteins which respond to lipid soluble chemical messengers that penetrate the cell. The receptor protein (specific for each hormone/regulator) is inherently capable of binding to specific genes, but its attached proteins HSP-90 and may be some others prevent it from adopting the configuration needed for binding to DNA.