Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

PRINCIPLES OF GENERAL PHRAMACOLOGY

Pharmacology: Pharmacology is the science of drugs.

Pharmacodynamics: It is a branch of Pharmacology includes study of physiological and biochemical effects of drugs and their mechanism of action at organ system/subcellular/ macromolecular levels.

Pharmacokinetics: This refers to movement of drug in and alteration of the drug by the body; includes absorption, distribution, biotransformation and excretion of the drug.

Drug: It is the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment/cure of a disease.

Pharmacotherapeutics: It is the application of pharmacological information together with knowledge of the disease for its prevention, mitigation or cure.

Sources of drugs: Drugs can be obtained from various sources like plants, animals, minerals, microorganisms, organic sources.

Drug Nomenclature:

A drug generally has three categories of names:

Chemical name: It describes the substance chemically,

Non-proprietary (generic) name: It is name accepted by competent scientific authority.

Proprietary (Brand) name: It is the name assigned by the manufacturer(s).

Essential drug concept: They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost effectiveness.

Orphan Drugs:

These are drugs or biological products for diagnosis/treatment prevention of a rare disease.

References

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology.**

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ROUTES OF DRUG ADMINISTRATION: INTRODUCTION AND CLASSIFICATION

Enteral (Through Alimentary tract)

- Oral
- Sublingual or buccal
- Rectal

Parenteral (Through Injection)

- Intravenous
- Intramuscular
- Subcutaneous
- Intradermal
- Intraperitoneal
- Intrapleural
- Intracardiac
- Intra-arterial
- Intrathecal
- Intra-articular

Local Routes:

- Topical
- Inhalation

Factors for choice of routes of administration

- Physical and chernical properties of the drug (solid/liquid/ gas; solubility, stability, pH, irritancv).
- Site of desired action-localized and approachable or generalized and not approachable.
- Rate and extent of absorption of the drug from different routes.
- Effect of digestive juices and first pass metabolism on the drug.
- Rapidity with which the response is desired (routine treatment or emergency).
- Accuracy of dosage required (i.v. and inhalational can provide fine tuning).
- Condition of the patient (unconscious, vomiitting)

References

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**
3. **Tripathi K.D.: Essentials of Medical Pharmacology**

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MERITS AND DEMERITS OF VARIOUS ROUTES OF DRUG ADMINISTRATION

Oral Route:

Merits:

- Commonest, Safest, Convenient
- No skill required, self medication
- Painless, & acceptable, Cost effective
- No maximal/strict sterilization required
- Due to slow rate of absorption adverse effects occurs less
- Large volume (doses) can be given
- Systemic / local effects in G.I.T

De-merits

- Absorption varies (delay, decrease, or increase)
- Irritation of gastric mucosa
- Patient compliance not ensured
- First pass metabolism
- Metabolism of drug (to inactive form)

Parenteral Route:

Merits:

- Rapid onset of action
- useful in emergency
- No first pass effect, 100% bioavailability,
- Dose more accurately delivered & give smooth effective
- Suitable in vomiting , motion sickness, migraine, unconscious patients, or when a patient can not swallow , & when cooperation is lacking
- Large volume (doses) of drug can be given

Demerits:

- More chances of adverse effects, most dangerous
- Maximal Sterilization, chances of infection,
- Skill, no self medication
- Local irritation at site of administration

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**

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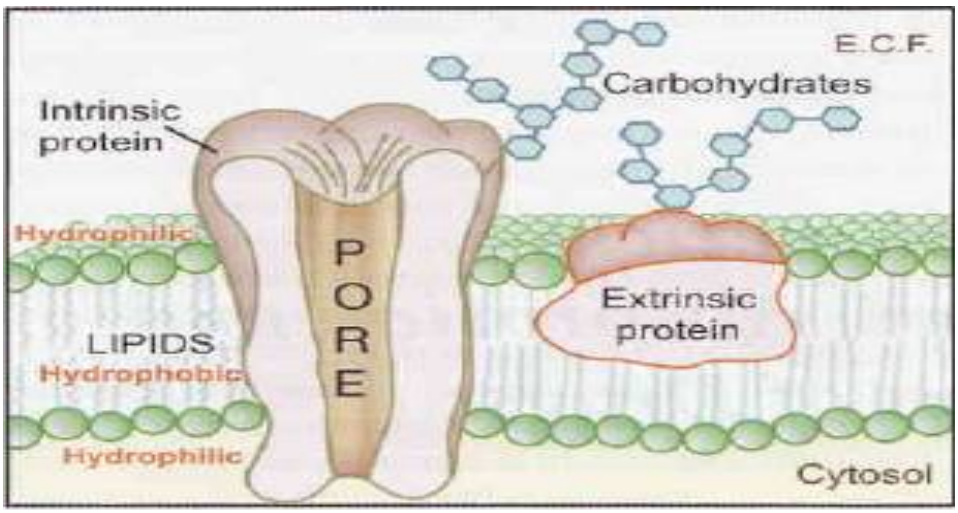
BIOLOGICAL MEMBRANES- STRUCTURE AND TYPES

Biological membrane:

This is a bilayer of phospholipid and cholesterol molecules, the polar groups of these are oriented at the two surfaces and the non polar hydrocarbon chains are embedded in the matrix to form a continuous sheet. Extrinsic and intrinsic protein molecules are adsorbed on the lipid bilayer. Glycoproteins or glycolipids are formed on the surface by attachment to polymeric sugars, amino sugars or sialic acids. Pores and paracellular spaces or channels also exist between certain epithelial /endothelial cells.



References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**
3. **Katzung B.G.: Basic and Clinical Pharmacology**
4. **Tripathi K.D.: Essentials of Medical Pharmacology**
5. **Robins: Textbook of Pathology.**

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PROPERTIES AND FUNCTIONS OF BIOLOGICAL MEMBRANES

- Cell membranes are relatively permeable to water either by diffusion or by flow resulting from hydrostatic or osmotic differences across the membrane, and bulk flow of water can carry with it drug molecules.
- Proteins with drug molecules bound to them are too large and polar for this type of transport to occur; thus, transmembrane movement generally is limited to unbound drug.
- Paracellular transport through intercellular gaps is sufficiently large that passage across most capillaries is limited by blood flow and not by other factors. This type of transport is an important factor in filtration across glomerular membranes in the kidney.
- Important exceptions exist in such capillary diffusion, however, because "tight" intercellular junctions are present in specific tissues, and paracellular transport in them is limited. Capillaries of the central nervous system (CNS) and a variety of epithelial tissues have tight junctions.
- Bulk flow of water can carry with it small water-soluble substances, but bulk-flow transport is limited when the molecular mass of the solute exceeds 100 to 200 daltons. Accordingly, most large lipophilic drugs must pass through the cell membrane itself.

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**
3. **Katzung B.G.: Basic and Clinical Pharmacology**
4. **Tripathi K.D.: Essentials of Medical Pharmacology**
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PHYSICOCHEMICAL FACTORS AND PROCESSES IN TRANSFER OF DRUGS ACROSS THE BIOLOGICAL MEMBRANES

Physicochemical factors in transfer of drugs across the biological membranes

The absorption, distribution, metabolism, and excretion of a drug all involve its passage across cell membranes. Mechanisms by which drugs cross membranes and the physicochemical properties of molecules and membranes that influence this transfer are critical to understanding the disposition of drugs in the human body. The characteristics of a drug that predict its movement and availability at sites of action are its molecular size and shape, degree of ionization, relative lipid solubility of its ionized and nonionized forms, and its binding to serum and tissue proteins.

In most cases, a drug must traverse the plasma membranes of many cells to reach its site of action. Although barriers to drug movement may be a single layer of cells or several layers of cells and associated extracellular protein, the plasma membrane represents the common barrier to drug distribution.

Processes in transfer of drugs across the biological membranes

Passive diffusion: The drug diffuses across the membrane in the direction of its concentration gradient.

Filtration: Filtration is passage of drugs through aqueous pores in the membrane or through paracellular spaces.

Specialized transport: This can be carrier mediated or by pinocytosis.

Carrier transport: Carrier transport is specific for the substrate and competitively inhibited by analogues which utilize the same transporter.

Depending on requirement of energy, carrier transport is of two types:

- **Facilitated diffusion**
- **Active transport**

Pinocytosis: Process of transport across cell in particulate form by formation of vesicles, applicable to proteins and other big molecules

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**

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DRUG ABSORPTION AND FACTORS AFFECTING DRUG ABSORPTION

Absorption is a process by which a drug travels from its site of administration into bloodstream.

Factors affecting drug absorption:

Method of administration: Drugs administered by the parenteral or the inhalation route have to cross only a few layers of cells to reach systemic circulation as compared to the drugs administered orally.

Blood flow to the absorption site: Increased blood flow at the site of absorption facilitates absorption resulting in rapid onset of action.

Drug-drug Interactions: Interactions between two or more drugs can alter the absorption scheme of a drug reducing intensity of the response produced.

Food drug interactions: Presence of food can also affect absorption of certain drugs. E.g. grapefruit juice decreases the absorption of many drugs like benzodiazepines, sedatives etc.

Emotional factors: Emotional factors like stress, trauma, depression, excitement have been reported to affect the absorption of drugs.

Formulation factors: Drugs formulated in the form of a solution report better absorption profiles as compared to solid dosage forms.

Intestinal Motility: Increased intestinal motility brings the drug in more intimate contact with its surfaces, facilitating better absorption.

First pass effect: First pass effect significantly reduces the total amount of the drug that finally reaches the systemic circulation.

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**
3. **Katzung B.G.: Basic and Clinical Pharmacology**
4. **Tripathi K.D.: Essentials of Medical Pharmacology**

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BIO-AVAILABILITY AND FACTORS AFFECTING DRUG BIO-AVAILABILITY

Bioavailability is defined as the amount of the drug that reaches the systemic circulation. It is a parameter that provides information about the absorption profile of the drug. It is said that efficacy of a drug depends on the amount of the drug absorbed and the rate at which it is absorbed.

Factors affecting drug absorption:

Physicochemical properties of the drug molecule:

Pka: From the pH partition hypothesis, it is said that the non-ionized form of the drug is better absorbed as compared to the ionized form.

Drug solubility: Drugs with high aqueous solubility show better absorption profile as compared to drugs having low aqueous solubility.

pH: pH plays an important role as some drugs are destroyed due to highly acidic pH of stomach.

Particle Size: Drug molecules having smaller particle size have larger effective surface area. Particle size is critical for drugs having low aqueous solubility.

Formulation or Pharmaceutical factors: presence of excipients:

Presence of excipients may influence process of absorption and bioavailability as certain excipients slower process of absorption.

Physiological factors:

Age: Especially observed in the elderly because of reduced efficiency in functioning of organs.

Food- drug interactions: Chemical reactions occur between food and the drugs results in destruction in some portion of the drug.

Drug- drug interactions: Ranitidine affects the absorption of drugs like Warfarin.

First pass metabolism: It reduces amount of dose that reaches systemic circulation and therefore reduces bioavailabilty.

References:

1. **Katzung B.G.: Basic and Clinical Pharmacology**
2. **Tripathi K.D.: Essentials of Medical Pharmacology**

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DRUG DISTRIBUTION AND FACTORS AFFECTING DRUG DISTRIBUTION

Distribution is a process by which the drug is transported to the different target organs or body tissues after it is absorbed systemically. It is important for the drug to be present in the required concentration at the site of action to initiate a therapeutic response. It explains the extent to which drug reaches different body tissues and also about its sites.

Factors affecting drug distribution:

Blood flow to the organ: Drug upon distribution rapidly diffuses and distributes itself into organs with a good blood supply. Distribution into moderately & poorly perfused areas occurs at gradual rate.

Solubility characteristics of the drug: The solubility of a drug plays an important role in distribution as the drug has to cross the cell membranes to be distributed throughout the body.

Organ size: Size of the organ may affect the amount of the drug distributed and retained by them.

Plasma protein binding: Only unbound form of drug produces therapeutic effect due to its ability to cross the cell membranes easily.

Presence of anatomic barriers:

Blood Brain barrier: Drug molecules with a specific molecular size and good lipid solubility cross this barrier passive transport or by transporter.

Blood -Cerebrospinal barrier: The permeability of drug molecules through the junctions of this barrier is slightly more as compared to the blood brain barrier.

Placental Barrier: This barrier helps in the transportation of nutrients and gases from the mother to the fetus.

Drug redistribution: Distribution of drugs is immediate to regions receiving high blood flow such as the brain, heart where as distribution is gradual to regions receiving low blood flow.

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Katzung B.G.: Basic and Clinical Pharmacology**
3. **Tripathi K.D.: Essentials of Medical Pharmacology**

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DRUG METABOLISM AND FACTORS AFFECTING DRUG METABOLISM

Metabolism is defined as a process that involves breakdown of drugs into a form that can be easily eliminated out of the body. It involves use of various enzymes to bring about the conversion from one chemical form to another. Metabolism occurs mainly in liver.

Significance of metabolism:

To facilitate drug excretion or drug elimination: The water soluble form of drug can be easily eliminated. Metabolism helps in this conversion resulting in generation of a polar (water soluble) metabolite that can be readily excreted.

For pro-drugs: A pro-drug is a drug that is administered in a pharmacologically inactive form. It is metabolised in body to an active form to generate a pharmacologic response.

Helps in detoxification process: Metabolism helps to deactivate or detoxify certain potent drugs by converting them into metabolites that are less active or inactive in nature.

Phase I (non-synthetic reactions)

Oxidation: The reactions involve addition of oxygen atom or removal of H atom.

Reduction: Nitro and azo compounds undergo reduction in the presence of cytochrome P-450 enzymes.

Hydrolysis: Amides, esters undergo hydrolysis in presence of enzymes like amidases or esterases present in the liver.

Phase II reactions (synthetic/conjugation reactions):

Involves interactions with the phase I metabolites. Groups like glucoronic acid, glutathione, glycine, glutamate, methyl or sulphates called as conjugating groups attach to the functional groups of phase I metabolites to increase the polarity of these drug molecules for easy excretion. The metabolites obtained at the end have no pharmacological action.

References:

1. **Rang H.P. and Dale M.M.: Pharmacology**
2. **Katzung B.G.: Basic and Clinical Pharmacolgy**

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DRUG EXCRETION AND FACTORS AFFECTING DRUG EXCRETION

Excretion is the passage out of systemically absorbed drug.

Modes of drug elimination:

Urine: It is the most important channel of excretion for majority of drugs

Faeces: Apart from the unabsorbed fraction most of the drug present in faeces is derived from bile. Relatively larger molecules are preferentially eliminated in the bile.

Exhaled air Gases:

General anaesthetics, paraldehyde, alcohol are eliminated by lungs, irrespective of their lipid solubility.

Saliva and sweat: These are of minor importance for drug excretion. Lithium, pot. iodide, rifampin and heavy metals are present in these secretions in significant amounts.

Milk: The excretion of drug in milk is not important for the mother, but the suckling infant inadvertently receives the drug.

Factors affecting excretion of drugs:

Age: In the elderly, wear and tear of organs reduce the efficiency of drug elimination. For infants, the organs are still premature and this slows down the rate of removal of drug substances from the body.

Disease States: The presence of a disease reduces the efficiency of the excretion process. This results in accumulation of the drug in the body responsible for generating toxic effects. **Drug interactions:** Administration of multiple medications at a time may cause alterations in the time required to excrete the drugs from the body as both the drugs may compete to be eliminated from the body by the same mechanism.

pH of the urine: The pH of the urine also regulates the removal of drug substances from the body through ionization.

References:

1. **Rang H.P. and Dale M.M.: Pharmacology**
2. **Katzung B.G.: Basic and Clinical Pharmacology**
3. **Tripathi K.D.: Essentials of Medical Pharmacology**

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BASIC CONCEPTS OF CLINICAL PHARMACOKINETICS

The fundamental tenet of clinical pharmacokinetics is that a relationship exists between the pharmacological effects of a drug and an accessible concentration of the drug (*e.g.,* in blood or plasma). This relationship has been documented for many drugs and is of benefit in the therapeutic management of patients. For some drugs, no clear or simple relationship has been found between pharmacological effect and concentration in plasma, whereas for other drugs, routine measurement of drug concentration is impractical as part of therapeutic monitoring. In most cases, the concentration of drug at its sites of action will be related to the concentration of drug in the systemic circulation. The pharmacological effect that results may be the clinical effect desired, a toxic effect, or in some cases an effect unrelated to the known therapeutic efficacy or toxicity.

Clinical pharmacokinetics attempts to provide both a quantitative relationship between dose and effect and a framework within which to interpret measurements of concentrations of drugs in biological fluids for the benefit of the patient. The importance of pharmacokinetics in patient care is based on the improvement in therapeutic efficacy and the avoidance of unwanted effects that can be attained by application of its principles when dosage regimens are chosen and modified.

The physiological and pathophysiological variables that dictate adjustment of dosage in individual patients often do so as a result of modification of pharmacokinetic parameters. The four most important parameters governing drug disposition are *clearance,* a measure of the body's efficiency in eliminating drug; *volume of distribution,* a measure of the apparent space in the body available to contain the drug; *elimination half-life,* a measure of the rate of removal of drug from the body; and *bioavailability*, the fraction of drug absorbed as such into the systemic circulation.

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Tripathi K.D.: Essentials of Medical Pharmacology**

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CLINICAL PHARMACOKINETICS WITH REFERENCE TO CLEARANCE, VOLUME OF DISTRIBUTION AND HALF LIFE

Clearance: Clearance is the most important concept to consider when designing a rational regimen for long-term drug administration. The clinician usually wants to maintain steady-state concentrations of a drug within a *therapeutic window* associated with therapeutic efficacy and a minimum of toxicity for a given agent. Assuming complete bioavailability, the steady-state concentration of drug in the body will be achieved when the rate of drug elimination equals the rate of drug administration.

The concept of clearance is extremely useful in clinical pharmacokinetics because its value for a particular drug usually is constant over the range of concentrations encountered clinically.

Volume of distribution: Volume is a second fundamental parameter that is useful in considering processes of drug disposition. The volume of distribution (*V*) relates the amount of drug in the body to the concentration of drug (*C*) in the blood or plasma depending on the fluid measured. A drug's volume of distribution therefore reflects the extent to which it is present in extravascular tissues and not in the plasma.

The volume of distribution may vary widely depending on the relative degrees of binding to high-affinity receptor sites, plasma and tissue proteins, the partition coefficient of the drug in fat, and accumulation in poorly perfused tissues. As might be expected, the volume of distribution for a given drug can differ according to patient's age, gender, body composition, and presence of disease.

Half life: The half-life ($t_{½}$) is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%. The relevance of a particular half-life may be defined in terms of the fraction of the clearance and volume of distribution that is related to each half-life and whether plasma concentrations or amounts of drug in the body are best related to measures of response.

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Tripathi K.D.: Essentials of Medical Pharmacology**

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CLINICAL PHARMACOKINETICS WITH REFERENCE TO BIOAVAILABILITY

Bioavailability: It is important to distinguish between the rate and extent of drug absorption and the amount of drug that ultimately reaches the systemic circulation. The amount of the drug that reaches the systemic circulation depends not only on the administered dose but also on the fraction of the dose that is absorbed and escapes any first-pass elimination. This fraction is the drug's bioavailability.

If the hepatic blood clearance for the drug is large relative to hepatic blood flow, the extent of availability will be low when the drug is given orally (*e.g.,* lidocaine or propranolol). This reduction in availability is a function of the physiological site from which absorption takes place, and no modification of dosage form will improve the availability under conditions of linear kinetics. Incomplete absorption and/or intestinal metabolism following oral dosing will, in practice, reduce this predicted maximal value of *F*.

Although the rate of drug absorption does not, in general, influence the average steady-state concentration of the drug in plasma, it may still influence drug therapy. If a drug is absorbed rapidly (*e.g.,* a dose given as an intravenous bolus) and has a small "central" volume, the concentration of drug initially will be high. It will then fall as the drug is distributed to its "final" (larger) volume. If the same drug is absorbed more slowly, it will be distributed while it is being administered, and peak concentrations will be lower and will occur later. Controlled-release preparations are designed to provide a slow and sustained rate of absorption in order to produce smaller fluctuations in the plasma concentration–time profile during the dosage interval compared with more immediate-release formulations.

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**
3. **Katzung B.G.: Basic and Clinical Pharmacology**
4. **Tripathi K.D.: Essentials of Medical Pharmacology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

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BASIC CONCEPTS AND GENERAL DISCUSSION ON NONLINEAR PHARMACOKINETICS

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BASIC CONCEPTS OF THERAPEUTIC DRUG MONITORING (TDM)

Criteria for TDM:

1. **Assay methods**
2. **Narrow therapeutic range**
3. **Poor relationship between dose and serum drug concentrations (SDC)**
4. **Non-linear pharmacokinetics**
5. **Good relationship between serum SDC and therapeutic/toxic effects**
6. **Lack of therapeutic effects is dangerous**
7. **Difficulty in interpreting signs and symptoms of toxicity or therapeutic failure or in evaluating therapeutic responses: Toxicity vs therapeutic failure**

Methods of therapeutic drug monitoring

1. **EMIT: highly automated, rapid turnaround, many assays available, homogenous,**
2. **ELISA: highly automated, rapid turn around, moderate sensitivity but few assays available, heterogenous**
3. **RIA: high sensitivity but long turnaround,many interferences, heterogenous, radiation hazards**

Uses of therapeutic drug monitoring

1. **Maximizing & speeding up efficacy**
2. **Minimizing toxicity**
3. **Patient's drug history uncertain**
4. **Poor response to initial Rx or deterioration after good response**
5. **When hepatic or renal function is changing**
6. **During drug interactions**
7. **Individualizing therapy and dosage regimen adjustment**
8. **To make decision about future therapy**
9. **Pharmacokinetic profiling**

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**
3. **Bajaj and Gupta, clinical Pharmacy**
4. **Tripathi K.D.: Essentials of Medical Pharmacology**

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SITE AND MECHANISMS OF DRUG ACTION

Mechanism of drug action:

The effects of most drugs result from their interaction with macromolecular components of the organism. These interactions alter the function of the pertinent component and thereby initiate the biochemical and physiological changes that are characteristic of the response to the drug. The term *receptor* denotes the component of the organism with which the chemical agent is presumed to interact.

The notion that the receptor for a drug can be any functional macromolecular component of the organism has several fundamental corollaries. One is that a drug potentially is capable of altering both the extent and rate at which any bodily function proceeds. Another is that drugs do not create effects but instead modulate intrinsic physiological functions.

Sites of drug action:

Because drugs act by altering the activities of their receptors, the sites at which a drug acts and the extent of its action are determined by the location and functional capacity of its receptors. Selective localization of drug action within an organism therefore does not necessarily depend on selective distribution of the drug.

If a drug acts on a receptor that serves functions common to most cells, its effects will be widespread. If the function is a vital one, the drug may be particularly difficult or dangerous to use. Nevertheless, such a drug may be important clinically. If a drug interacts with receptors that are unique to only a few types of differentiated cells, its effects are more specific.

References:

1. **Rang H.P. and Dale M.M.: Pharmacology**
2. **Katzung B.G.: Basic and Clinical Pharmacology**
3. **Tripathi K.D.: Essentials of Medical Pharmacology**

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STRUCTURE ACTIVITY RELATIONSHIP (SAR)

The strength of the reversible interaction between a drug and its receptor, as measured by their dissociation constant, is defined as the *affinity* of one for the other. Both the affinity of a drug for its receptor and its intrinsic activity are determined by its chemical structure. This relationship frequently is quite stringent. Relatively minor modifications in the drug molecule may result in major changes in its pharmacological properties based on altered affinity for one or more receptors.

Exploitation of structure–activity relationships on many occasions has led to the synthesis of valuable therapeutic agents. Because changes in molecular configuration need not alter all actions and effects of a drug equally, it is sometimes possible to develop a congener with a more favorable ratio of therapeutic to adverse effects, enhanced selectivity among different cells or tissues, or more acceptable secondary characteristics than those of the parent drug. Therapeutically useful antagonists of hormones or neurotransmitters have been developed by chemical modification of the structure of the physiological agonist. Minor modifications of structure also can have profound effects on the pharmacokinetic properties of drugs.

Advances in molecular modeling of organic compounds and the methods for drug target (receptor) discovery and biochemical measurement of the primary actions of drugs at their receptors have enriched the quantitation of structure–activity relationships and its use in drug design. The importance of specific drug–receptor interactions can be evaluated further by analyzing the responsiveness of receptors that have been selectively mutated at individual amino acid residues. Such information increasingly is allowing the optimization or design of chemicals that can bind to a receptor with improved affinity, selectivity, or regulatory effect. Similar structure-based approaches also are used to improve pharmacokinetic properties of drugs, particularly with respect to knowledge of their metabolism. Advances in combinatorial chemistry contribute to structure-motivated drug design through powerful, if random, generation of new drugs.

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**

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DRUG RECEPTORS- BASIC DISCUSSION ABOUT RECEPTORS

The term *receptor* has been used operationally to denote any cellular macromolecule to which a drug binds to initiate its effects. Among the most important drug receptors are cellular proteins, whose normal function is to act as receptors for endogenous regulatory ligands—particularly hormones, growth factors, and neurotransmitters. The function of such physiological receptors consists of binding the appropriate endogenous ligand and, in response, propagating its regulatory signal in the target cell.

Identification of the two functions of a receptor, ligand binding and message propagation (*i.e.,* signaling), correctly suggests the existence of functional domains within the receptor: a *ligand-binding domain* and an *effector domain*.

The regulatory actions of a receptor may be exerted directly on its cellular target(s), *effector protein(s),* or may be conveyed by intermediary cellular signaling molecules called *transducers*. The receptor, its cellular target, and any intermediary molecules are referred to as a *receptor–effector system* or *signal-transduction pathway*. Frequently, the proximal cellular effector protein is not the ultimate physiological target but rather is an enzyme or transport protein that creates, moves, or degrades a small metabolite known as a *second messenger*. Second messengers can diffuse in the proximity of their binding sites and convey information to a variety of targets, which can respond simultaneously to the output of a single receptor binding a single agonist molecule.

Receptors and their associated effector and transducer proteins also act as integrators of information as they coordinate signals from multiple ligands with each other and with the metabolic activities of the cell.

An important property of physiological receptors that also makes them excellent targets for drugs is that they act catalytically and hence are biochemical signal amplifiers. The catalytic nature of receptors is obvious when the receptor itself is an enzyme, but all known physiological receptors are formally catalysts.

References:

1. **Rang H.P. and Dale M.M.: Pharmacology**
2. **Katzung B.G.: Basic and Clinical Pharmacology**
3. **Tripathi K.D.: Essentials of Medical Pharmacology**

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CLASSIFICATION AND FAMILIES OF RECEPTORS

Classification of receptors:

1. **G-protein coupled receptors:** E.g. opioid and dopaminergic receptors situated in the brain.
2. **Ion channel receptors:**
    a. **Ligand-gated ion channel receptor:** E.g. Nicotinic Acetylcholine receptor, GABA receptor.
    b. **Voltage-dependent ion channel receptor:** E.g. receptors in the cardiac or skeletal muscle cells are of this type.
3. **Enzyme linked receptors:**
    a. Intrinsic enzyme receptors
    b. JAK-STAT-Kinase binding receptors
4. **Nuclear receptors:** E.g. Steroidal receptors

G-protein coupled receptors:

These are a large family of cell membrane receptors which are linked to the effector through one or more GTP-activated proteins (G-proteins) for response effectuation. The receptor molecule has 7 α-helical membrane spanning hydrophobic amino acid (AA) segments which run into 3 extracellular and 3 intracellular loops.

Ion channel receptors:

These cell surface receptors, also called ligand gated ion channels, enclose ion selective channels within their molecules. The receptor is usually a pentameric protein, all subunits have four membrane spanning domains.

Enzyme linked receptors:

This class of receptors have a subunit with enzvmatic property or bind a JAK (Janus-Kinase) enzyme on activation. The agonist binding site and the catalytic site lie respectively on the outer and inner face of the plasma membrane.

Nuclear receptors: These are intracellular (cytoplasmic or nuclear) soluble proteins which respond to lipid soluble chemical messengers that penetrate cell.

References:

1. **Rang H.P. and Dale M.M.: Pharmacology**
2. **Tripathi K.D.: Essentials of Medical Pharmacology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

DRUG EFFECTS AND REGULATION OF RECEPTORS

Receptors not only initiate regulation of biochemical events and physiological functions but also are themselves subject to many regulatory and homeostatic controls. These controls include regulation of the synthesis and degradation of the receptor by multiple mechanisms, covalent modification, association with other regulatory proteins, and/or relocalization within the cell. Transducer and effector proteins are regulated similarly. Modulating inputs may come from other receptors, directly or indirectly, and receptors are almost always subject to feedback regulation by their own signaling outputs.

Continued stimulation of cells with agonists generally results in a state of *desensitization* (also referred to as *adaptation, refractoriness,* or *down-regulation*) such that the effect that follows continued or subsequent exposure to the same concentration of drug is diminished. This phenomenon known as *tachyphylaxis.*

Desensitization can be the result of temporary inaccessibility of the receptor to agonist or the result of fewer receptors synthesized and available at the cell surface. Down-regulation of receptor number best describes this latter accommodation of the cell to the chronic presence of excess agonist.

Feedback inhibition of signaling may be limited to output only from the stimulated receptor, a situation known as *homologous desensitization*. Attenuation extending to the action of all receptors that share a common signaling pathway is called *heterologous desensitization*.

Predictably, supersensitivity to agonists also frequently follows chronic reduction of receptor stimulation. Supersensitivity can be the result of tissue response to pathological conditions such as happens in cardiac ischemia and is due to synthesis and recruitment of new receptors to the surface of the myocyte.

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**
3. **Tripathi K.D.: Essentials of Medical Pharmacology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

QUANTITATION OF DRUG RECEPTOR INTERACTIONS AND THEIR EFFECTS

Affinity: It is defined as the ability of the drug substance to attach itself to the receptor to form a drug- receptor complex.

Intrinsic activity: The ability of the drug molecule to stimulate the receptor and initiate changes (produce action) when it binds to it.

Agonist: An agonist is defined as an agent that binds to the receptor, forms a drug –receptor complex and evokes a biological response similar as its endogenous ligand.

Antagonist: An antagonist is defined as an agent that binds to the receptor but does not have the ability/capacity to evoke/elicit a biological response similar to the agonist.

Partial Agonist: A partial agonist is defined as an agent that has affinity towards the receptor and therefore binds to it but elicits a response lesser/lower than that produced by the full agonist.

Inverse Agonist: An inverse agonist is defined as an agent that binds to the receptor but produces a response that opposite to that of an agonist.

Silent Receptors: Silent receptors are those receptors that are not capable eliciting any response even after the agonists bind to them.

Spare Receptors: The receptors which are present more in number than those receptors needed to produce the optimum pharmacological effect are called as spare receptors.

Competitive Antagonist: A competitive antagonist is an agent that competes with the agonist to bind to the receptor and succeeds in attaching itself to the receptor due to being present in a relatively higher concentration compared to the agonist.

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**
3. **Katzung B.G.: Basic and Clinical Pharmacology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

DOSE RESPONSE RELATIONSHIPS AND THERAPEUTIC INDEX

The concept of dose response curves provides a foundation to understand the action of most drugs. The dose is plotted on the X- axis, while the response of the drug on the Y- axis. This results in a hyperbola. The curve obtained is sigmodal in shape, but it can also be linear, concave or convex. The central portion of the curve is linear and helps in calculating the slope and other functions relatively easily. The slope of the curve indicates change in response with variations in dose. Generally, an increase in dose would increase response, but this relationship is observed only to a particular extent. Thereafter, the same effect is observed for any increase in dose.

Efficacy: The ability of a drug to produce a maximum response (100%) is called efficacy. It is a qualitative aspect defining the activity of the drug.

Ceiling effect: It is highest point on the DRC. It is the maximum response produced by a particular dose of the drug.

Potency: It is defined as the dose of the drug required to produce a particular effect.

Therapeutic Range: It represents the ranges of doses with their upper and lower limits for which the administered drugs would render maximum therapeutic benefit and minimum side effects to the patients.

Therapeutic index: Therapeutic index, also called as therapeutic ratio is expressed as the ratio of LD50 to ED50. LD stands for the lethal dose and hence LD50 is the lethal dose of the drug that kills 50%o f the animals. ED stands for effective dose and hence ED50 is the dose of the drug that produces therapeutic response in 50% of the animals.

Therapeutic index= Max. tolerated drug concentration / Min. effective drug concentration.

References:

1. **Rang H.P. and Dale M.M.: Pharmacology**
2. **Katzung B.G.: Basic and Clinical Pharmacology**
3. **Tripathi K.D.: Essentials of Medical Pharmacology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

COMBINED EFFECT OF DRUGS

When two or more drugs are given simultaneously or in quick succession they may be either indifferent to each other or exhlbit synergism or antagonism. The interaction may take place at pharmacokinetic level or at pharmacodynamic level.

Synergism: When the action of one drug is facilitated or increased by the other, they are said to be synergistic. Synergism can be:

Additive: The effect of the two drugs is in the same direction and simply adds up: effect of drugs A + B = effect of drug A + effect of drug B

Supraadditive (potentiation): The effect of combination is greater than individual effects of components: effect of drug A + B > effect of drug A +effect of drug B

Antagonism:

When one drug decreases or abolishes the action of another, they are said to be antagonistic: effect of drugs A + B < effect of drug A + effect of drug B. Depending on the mechanism involved, antagonism maybe:

Physical antagonism Based on the physical property of the drugs, e.g. charcoal adsorbs alkaloids and can prevent their absorption-used in alkaloidal poisonings.

Chemical antagonism: Two drugs react chemically and form an inactive product.

Physiological/functional antagonism: The two drugs act on different receptors or by different mechanisms, but have opposite overt effects on same physiological function.

Receptor antagonism: One drug blocks the receptor action of the other.

Receptor antagonism can be competitive or noncompetitive.

Competitive antagonism (equilibrium type): The antagonist competes with it and binds to the same site to the exclusion of the agonist molecules.

Noncompetitive antagonism: The antagonist binds to a different allosteric site altering receptor in such a way that it is unable to combine with agonist.

Non equilibrium (competitive) antagonism: Certain antagonists bind to the receptor with strong bonds or dissociate from it slowly.

References:

1. **Rang H.P. and Dale M.M.: Pharmacology**
2. **Tripathi K.D.: Essentials of Medical Pharmacology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

ADVERSE DRUGS REACTIONS (ADR)

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

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DRUG TOXICITY (TERATOGENECITY, CARCINOGENECITY, MUTAGENECITY), IATROGENIC DISEASES

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

DRUG REGULATION AND DEVELOPMENT

The drug development process starts with the synthesis of novel chemical compounds. As more insight is gained into structure–activity relationships, the search for new agents becomes more clearly focused.

Preclinical testing:

It yields information on the biological effects of new substances.

Biochemical-pharmacological investigations: Effects of drugs on receptor binding assays or experiments on cell cultures, isolated cells, and isolated organs.

Toxicological investigations: These serve to evaluate the potential for:

- Toxicity associated with acute or chronic administration
- Genetic damage (genotoxicity, mutagenicity)
- Production of tumors (oncogenicity or carcinogenicity);
- Causation of birth defects (teratogenicity).

In animals, compounds under investigation also have to be studied with respect to their pharmacokinetics.

Clinical testing:

Phase I studies: Done on healthy subjects to determine whether effects observed in animal experiments also occur in humans. Dose–response relationships are determined.

Phase II studies: Potential drugs are first tested on selected patients for therapeutic efficacy in those disease states for which they are intended. If a beneficial action is evident, and the incidence of adverse effects is acceptably small,

Phase III studies: Involving a larger group of patients in whom new drug will be compared with conventional treatments in terms of therapeutic outcome. These clinical trials are subject to review and approval by institutional ethics committees according to international codes of conduct.

Phase IV studies: After approval, new drug may be marketed under a trade name and become available for prescription by physicians and dispensing by pharmacists.

References:

1. **Lullman, Color atlas of Pharmacology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

BASIC DISCUSSION ON GENE TRANSFER TECHNOLOGIES, OBSTACLES

Gene therapy involves the efficient introduction of functional gene into the appropriate cells of the patient in order to produce sufficient amount of protein encoded by transferred gene (transgene) so as to precisely and permanently correct the disorder. Transgene can be transferred into the target cell by physical, chemical and viral vectors. New organ transplant or tissue implants, human artificial chromosome, receptor mediated delivery and virally directed enzyme prodrug therapy (VDEPT) are other advancements in the field of gene therapy.

There are three main strategies in gene therapy.

1. Gene addition.
2. Removal of a harmful gene by antisense nucleotide or ribozymes.

Approaches to gene therapy:

Ex-vivo approach where the target gene is taken out from the body and transgene is introduced into the cell and the cell is reimplanted into the human body. This approach is only applicable to the cells that are capable of reimplantation inside the human body e.g. lymphocytes, fibroblasts, myoblasts, umbilical cord blood, stem-cells, bone marrow cells, hepatocytes etc. In-vivo approach where the transgene is introduced into the target cell inside the body.

Pre-requisites for human gene therapy are:

1. Identification of the gene responsible for disease.
2. Cloning of the gene.
3. Identification of gene mutations.
4. Linkage of gene mutation to the pathophysiology of the disease.
5. Identification or selection of the gene transfer target cell.
6. Detection of gene expression and protein function.
7. Gene transfer efficacy and safety testing system.

References:

1. **Tripathi K.D.: Essentials of Medical Pharmacology**
2. **Subramanyam, Pharmaceutical bitechnology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

VIRAL VECTORS, NON-VIRAL DNA DELIVERY STRATEGIES

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

THERAPEUTIC PARADIGMS: GENE THERAPY FOR INHERITED DISORDERS

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

GENETIC REPAIR STRATEGIES, GENE INACTIVATION STRATEGIES

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

ECTOPIC SYNTHESIS THERAPEUTIC PROTEINS

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

DISEASE TARGETS FOR GENE THERAPY

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

DRUG TREATMENT IN PEDIATRIC AND GERIATRIC PATIENTS

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

DRUG TREATMENT IN PREGNANCY AND LACTATION

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

HAEMOPOIETICS- CLASSIFICATION AND PHARMACOLOGY

Iron

Iron forms the nucleus of the iron porphyrin heme ring, which together with globin chains forms hemoglobin that reversibly binds oxygen and provides the critical mechanism for oxygen delivery from lungs to other tissues. In the absence of adequate iron, small erythrocytes with insufficient hemoglobin are formed resulting in microcytic hypochromic anemia.

Treatment of iron deficiency anemia

Oral Iron Therapy:

Only ferrous salts should be used because of most efficient absorption. Ferrous sulfate, ferrous gluconate, ferrous fumarate are the most commonly used oral iron preparations.

Parenteral iron therapy:

Should be reserved for patient unable to tolerate or absorb oral iron.

Drugs for parenteral administration include: Iron dextran - Iron sorbitol

They may be given by deep IM or occasionally IV. Intravenous administration may result in very severe allergic reactions and thus should be avoided if possible.

Vitamin B12

Vitamin B12 is made up of a porphyrin-like ring with a central cobalt atom attached to a nucleotide. Daily vitamin B12 requirement is 2-5 mg. It is mainly obtained from animal products and serves as a co factor for essential biochemical reaction in humans. Ultimate source of vit B12 is from microbial synthesis.

Folic acid

Folic acids are required for essential biochemical reactions that provide precursors for the synthesis of amino acids, purines and DNA.Daily requirement is 50 -100µg. Folic acid deficiency is not uncommon.

References:

1. **Rang H.P. and Dale M.M.: Pharmacology**
2. **Katzung B.G.: Basic and Clinical Pharmacology**
3. **Tripathi K.D.: Essentials of Medical Pharmacology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

COAGULANTS- CLASSIFICATION AND PHARMACOLOGY

Hemostasis is spontaneous arrest of bleeding from a damaged blood vessel. Steps: Vascular injury---- vasospasm---platelet adhesion---- platelet aggregation---coagulation cascades--- fibrin formation.

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ANTICOAGULANTS- CLASSIFICATION AND PHARMACOLOGY

Anticoagulants: are the drugs which inhibit fibrin formation.

Classification Based on mechanism of action:

1. **Fast and direct acting:** e.g: Heparin
2. **Slow and indirect acting:** Oral anticoagulants e.g Warfarin and Dicumarol

Heparin: It is a heterogeneous mixture of sulfated mucopolysaccharides

Mechanism of action: Heparin activates antithrobimin III (AT III) which inhibits clotting factor proteases hence it inhibits the formation of fibrin clots.

Clinical Uses: Prevention and treatment of venous thrombosis, atrial fibrillation with embolus formation, in arterial embolus, treatment of coronary occlusion, acute myocardial infarction and peripheral arterial embolism.

Administration: Can be given IV or subcutaneous. Oral therapy is ineffective.

Side effects: Bleeding, allergy, alopecia, osteoporosis and thrombocytopenia

Contraindications: Contraindicated in patients who are hypersensitive, suffering from hemophilia, thrombocytopenia, purpura, severe hypertension, intracranial hemorrhage, infective endocarditis etc.

Oral anticoagulants: It is the most widely used coumarin anticoagulant and may be considered to be the drug of choice as an oral anticoagulant.

Mechanism of action: The anticoagulant prevents reductive metabolism of the inactive vitamin K epoxide back to its active form

Clinical uses: Prevention and treatment of deep vein thrombosis, treatment of atrial fibrillation with thrombus formation, prevention and treatment of pulmonary embolus etc.

Side effects: Birth defect in pregnancy, hemorrhagic disease of newborn, hemorrhagic infarcts and cutaneous necrosis

Contraindications: drug should never be administered during pregnancy.

Drug interactions: The effect of warfarin will be increased when it is used with the drugs: Cimitidine, dsulfiram, metronidazole, phenylbutazone, ASA.

The effect of warfarin will be decreased when it is used with the drugs: Barbiturates, Cholestyramine, Rifampincin, Diuretics, vit K

References:

1. **Rang H.P. and Dale M.M.: Pharmacology**
2. **Katzung B.G.: Basic and Clinical Pharmacology**
3. **Tripathi K.D.: Essentials of Medical Pharmacology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

THROMBOLYTICS- CLASSIFICATION AND PHARMACOLOGY

Thrombolytic agents rapidly lyse thrombi by catalyzing the formation of plasmin from plasminogen. All thrombolytic agents currently in use act directly or indirectly as plasminogen activators.

The presently used plasminogen activators are:

Streptokinase: a protein synthesized by streptococci, combines with plasminogen to convert it to active plasmin.

Urokinase: human enzyme synthesized by the kidneys that directly converts plasminogne to active plasmin

Anistreptase: (Acylated plasminongen -streptokinase activator)- bacterial streptokinase plus human plasminogen

Tissue plaminogen activator (tPA): This activates preferentially plasminogen that is bound to fibrin.

Indications: Multiple pulmonary emboli, central deep vein thrombosis and acute myocardial infarction.

Adverse Reactions: Bleeding and allergic reactions are most common adverse effects thrombolytics.

Contra-indications: Severe hypertension, recent cranial trauma and history of cerebrovascular accident.

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**
3. **Katzung B.G.: Basic and Clinical Pharmacology**
4. **Tripathi K.D.: Essentials of Medical Pharmacology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

ANTIPLATELET AGENTS- CLASSIFICATION AND PHARMACOLOGY

Antiplatelet drugs:

Platelet function is regulated by three categories of substances

Agents outside the platelet that interact with platelet membrane receptors: e.g. catecholamines, prostacyclin

Agents generated within the platelets and interact with the membrane receptors: e.g. prostaglandin E2 and serotonin

Agents generated within the platelet and act within the platelet: e.g. thromboxane A2 and calcium ions

Antiplatelets act on any one of the above processes. They include aspirin, ticlopidine, dipyridamole.

Aspirin (Acetyl salicylic acid): Thromoboxane A2 is an arachidonate product that causes platelet to change shape, to release their granules and to aggregate. Aspirin antagonize this pathway interfere with platelet aggregation and prolong bleeding time at low dose. It inhibits the synthesis of thromboxane A2 by irreversible acetylation of the enzyme cyclo-oxygenase.

Therapeutic Uses: Prophylaxis against myocardial infarction and stroke,

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**
3. **Katzung B.G.: Basic and Clinical Pharmacology**
4. **Tripathi K.D.: Essentials of Medical Pharmacology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

DRUGS USED IN HYPERLIPIDEMIAS- CLASSIFICATION AND PHARMACOLOGY

Hyperlipidemia:

Elevated concentrations of lipid (hyperlipidemia) can lead to the development of atherosclerosis and CAD.

Statins: Lovastatin , fluvastatin , pravastatin , simvastatin ,atorvastatin

- These potent reversible competitive inhibitors of 3-hydroxy 3-methyl glutaryl coenzyme A reductase, rate-controlling enzyme in cholesterol biosynthesis.

Fibrates: Gemfibrozil , fenofibrate , clofibrate

- Increased LPL activity, increases clearance of VLDL & chylomicron in plasma.
- Increased FFA uptake by the liver.
- Decreased VLDL due to increased fatty acid metabolism
- Increased LDL-C uptake by the liver.
- Raises HDL cholesterol levels.
- Increase excretion of hepatic cholesterol in bile.

Niacin:

- In adipose tissue: decrease in free fatty acids mobilization.
- In liver: niacin inhibits hepatocyte diacylglycerol acyltransferase-2
- In plasma: it increases LPL activity, increases clearance of VLDL & chylomicron.
- Niacin also promotes hepatic apoA-I production.

Ezitimibe:

- Impairs dietary and biliary cholesterol absorption.
- Reducing the pool of cholesterol absorbed from the diet.
- Fall in measured LDL cholesterol.

Bile acid sequestrants:

- They bind to bile acids in the intestinal lumen, prevent their reabsorption and increase their excretion, thus interrupt the enterohepatic circulation of bile acids.

References:

1. **Rang H.P. and Dale M.M.: Pharmacology**
2. **Katzung B.G.: Basic and Clinical Pharmacology**
3. **Tripathi K.D.: Essentials of Medical Pharmacology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

AUTACOIDS- INTRODUCTION AND CLASSIFICATION

Autacoid:

- This term is derived from Creek: autos-self , akos-healing substance or remedy.
- These are diverse substances produced by a wide oariety of cells in the body, having intense biological activity, but generally act locally (e.g. within inflammatory pockets) at the site of synthesis and release.
- They have also been called 'local hormones'. However, they differ from 'hormones' in two important ways-hormones are produced by specific cells, and are transported through circulation to act on distant target tissues.
- Autacoids are involved in a number of phvsiological and pathological processes (especialiy reaction to injury and immunological insult) and even serve as transmitters or modulators in the nervous system, but their role at many sites is not precisely known. A number of useful drugs act by modifying their action or metabolism.

The classical autacoids are-

Amine autacoids: Histamine, S-Hydroxytryptamine (Serotonin)

Lipid derived autacoids: Prostaglandins, Leukotrienes, Platelet activating factor Peptide autacoids Plasma kinins (Bradykinin, Kallidin), Angiotensin

In addition, cytokines (interleukins, TNFU, GM-CSF etc.) and several peptides like gastrin, somatostatin, vasoactive intestinal peptide and many others may be considered as autacoids.

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**
3. **Katzung B.G.: Basic and Clinical Pharmacology**
4. **Tripathi K.D.: Essentials of Medical Pharmacology**
5. **Robins: Textbook of Pathology.**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

AUTACOID ANTAGONISTS- PHARMACOLOGY

Histamine:

Histamine is a potent tissue amine formed by decarboxylation of histidine and major portion is stored in mast cells and basophils.

Mechanisms of Action: It acts on 2 major types of receptors

Stimulation of H1 receptors: results in smooth muscle contraction, increased vascular permeability, and mucus production. These effects are blocked competitively by H1 antagonists.

Activation of H2 receptors: increases gastric acid production, and this effect is blocked by H2 blockers such as cimetidine.

Both types of receptors are involved in vascular dilatation and edema formation.

5-Hydroxytreptamine (Serotonin):

It is widely distributed in plants and animals. It is synthesized from the amino acid tryptophan and acts on several types of receptors.

Mechanism of action:

5-Hydroxytreptamine (Serotonin) shows its pharmacological activities by acting on 5-HT receptors. Four families of 5-HT receptors (5-HT1, 5-HT2, 5-HT3, 5-HT4-7) comprising of 14 receptor subtypes so far been recognized.

Prostaglandins:

They were named so because of their presumed origin from the prostate gland. Human seminal fluid is the richest known source, but they are also present in various tissues. The prostaglandins are synthesized from polyunsaturated fatty acids at their sites of action. PGE2 and PGF2 are the two main prostaglandins. They are released in the body by mechanical, chemical, and infectious insults.

They play an important role in the development of the inflammatory response in association with other mediators.

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**
3. **Katzung B.G.: Basic and Clinical Pharmacology**
4. **Tripathi K.D.: Essentials of Medical Pharmacology**

Class- *Second Year B. Pharm* ***Subject- Pharmacology-I***

Subject Incharge- *Miss. Pujari R. R.* ***Lecture Synopsis No.***

AUTACOID ANTAGONISTS- PHARMACOLOGY

Antihistaminic Drugs:

These drugs competitively block histamine receptors, are of two types:

H1 Receptor Antagonists:

Classification of H1 receptor antagonists:

1. Potent and sedative: diphenhydramine and promethazine.
2. Potent but less sedative: cyclizine and chlorpheniramine
3. Less potent and less sedative: pheniramine
4. Non-sedative: terfenadine, loratadine, and cetrizine.

The newer generation agents are relatively free of central depressant effects. These agents may also possess anti-emetic effects.

Pharmacological Actions:

Antihistaminic Actions: They block histamine effects at various sites.

Other Effects:

- Most of them produce CNS depression resulting in sedation, drowsiness, inability to concentrate, and disturbances of coordination. Agents like phenindamine may produce stimulation.
- Anti-motion sickness effects are exhibited by promethazine, diphenhydramine, and dimenhydinate. Promethazine and mepyramine have significant local anesthetic effect.
- Majority possess atropine-like effects. Some have central antimuscarinic actions useful in the treatment of Parkinsonism.

Serotonin Antagonists:

- **Methysergide:** blocks the actions of 5-HT on a variety of smooth muscles. It also has a weak direct vasoconstrictor effect. It is an effective prophylactic agent for migrainous headaches. But has no effect in treating acute attacks, even may worsen the condition.
- Adverse reactions include gastrointestinal irritation, drowsiness, vertigo, and psychic disturbances.

References:

1. **Goodman and Gillman: Pharmacological Basis of Therapeutics**
2. **Rang H.P. and Dale M.M.: Pharmacology**
3. **Tripathi K.D.: Essentials of Medical Pharmacology**