SHAMBHUNATH INSTITUTE OF PHARMACY
1st Sessional Examination 2019-2020
D.Pharm Final Year
Pharmacology and Toxicology

Time: 1:30 hrs. **M.M. 20**
Paper Code: 214206
Roll No:

Note: Attempt any **five** questions. **(5x4=20)**

1. Describe the term Pharmacology with their scopes.
2. Give the general mechanism of drug actions (GPCR).
3. Give the short note on factors affecting drug action.
4. Define the term absorption. Write the factors affecting drug absorption.
5. Short note on:
    a. cAMP Pathways
    b. IP3/DAG Pathways
6. Short note on:
    a. Drug Metabolism and renal Excretion.
    b. Drug Distribution

ANSWERS

Ans.1. Pharmacology with their scopes-

Pharmacology is the study of drugs. Drugs are chemicals that produce therapeutically useful effects. They modify functions of living organisms and are generally given to prevent, diagnose ,or cure diseases .Drugs are an essential part of patient care ,and safe usage of drugs requires a sound knowledge of their : mode of action ,side effect, toxicity, range of dosage, rate and route of excretion and interactions with other drugs.

Some important basic terms:

Pharmacology:- Pharmacology is defined as the science of drugs. The term is derived from Greek words pharmakon, meaning a drug and logos ,meaning a study. It includes knowledge about the sources of drugs, their absorption, distribution, metabolism and excretion, their mode of action or mechanism of action and their toxicity. Pharmacology has major subdivisions,Pharmacognosy,Pharmacy,Pharmacokinetics,,Pharmacodynamics,Pharmacotherapeutics,Therapeutics,Chemotherapy ,Toxicology etc.

Pharmacy- Pharmacy is the study of the preparation ,compounding and dispensing of medicines. It is the science and art of preparing a drug or drug combination ,in a suitable dosage form,fit for administration to the patient.The pharmacist concerned primarily with preparing,compounding and dispensing medicines upon the written order of a licensed medical practitioner.

Pharmacokinetics (Greek kinesis,means movement) is the study of the fate of drugs in the body,right from the time they enter the body until they,or their by-products,are eliminated from the body,or movement of drugs in the body. In other words this includes absorption, distribution ,metabolism and excretion of drugs. These studies are done both in animals and man ,and the data are essential for the safe use of drugs.

Pharmacodynamics- (Greek dynamics means force) is the experimental study of actions of drugs on the living organism,including their mode of action or mechanism of action. **Pharmacotherapeutics**(Greek therapeia means medical treatment)- Pharmacotherapeutics is the treatment of disease by means of drugs.It utilizes information on drugs obtained by pharmacodynamic studies.

Therapeutics- (Greek therapeutike,means medical practice)Therapeutics is the practical branch of medicine dealing with the science and art of the treatment of disease . Empirical therapeutics is therapy bases on clinical evidence that the drug is effective ,although the mechanism by which it act is unknown.

Chemotherapy according to the definition proposed by Paul Ehrlich ,deals with the use of drugs capable of inhibiting or destroying invading microbes ,parasites,or cancer cells,while having minimal effect on healthy living tissues.

Toxicology (Greek toxikon means poison)Toxicology is the science of poisons, their sources, chemical composition ,action, tests for detection and antidotes.It forms a major part of forensic and environmental medicine. All drugs are potential poisons when given in high doses.

Clinical toxicology deals with the detection, diagnosis and treatment of poisoning. **Pharmacognetics** is a relatively new field and deals with the study of genetically determined variationin drug response.

Clinical pharmacology is the division which deals with the pharmacological effects of drugs in man. It provides information about the usefulness, potency and toxicity of new drugs in humans .It is of great importance for the effective and safe use of drugs in man.

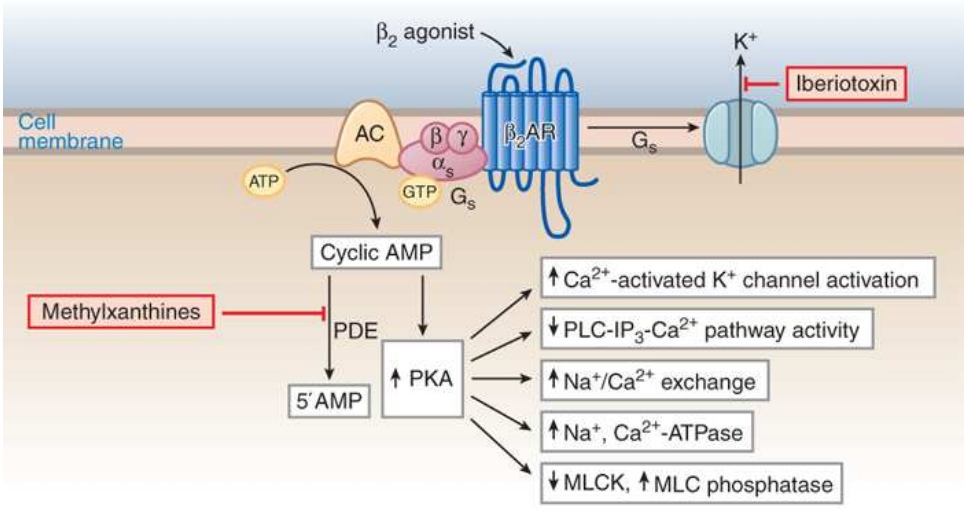
Ans.2. <u>General mechanism of drug actions-</u>

G protein-coupled receptors (GPCRs), also known as seven-(pass)-transmembrane domain receptors, 7TM receptors, heptahelical receptors, serpentine receptor, and G protein–linked receptors (GPLR), constitute a large protein family of receptors that detect molecules outside the cell and activate internal signal transduction pathways and, ultimately, cellular responses. Coupling with G proteins, they are called seven-transmembrane receptors because they pass through the cell membrane seven times.

G protein-coupled receptors are found only in eukaryotes, including yeast, choano flagellates and animals. The ligands that bind and activate these receptors include light-sensitive compounds, odors, pheromones, hormones, and neurotransmitters, and vary in size from small molecules to peptides to large proteins. G protein-coupled receptors are involved in many diseases.

There are two principal signal transduction pathways involving the G protein-coupled receptors:

- The cAMP signal pathway and
- The phosphatidylinositol signal pathway.



- **cAMP signal pathway-**

The cAMP signal transduction contains 5 main characters: stimulative hormone receptor (Rs) or inhibitory hormone receptor (Ri); stimulative regulative G-protein (Gs) or inhibitory regulative G-protein (Gi); adenylyl cyclase; protein kinase A (PKA); and cAMP phosphodiesterase.

Stimulative hormone receptor (Rs) is a receptor that can bind with stimulative signal molecules, while inhibitory hormone receptor (Ri) is a receptor that can bind with inhibitory signal molecules.

- **Phosphatidylinositol signal pathway-**

the phosphatidylinositol signal pathway, the extracellular signal molecule binds with the G-protein receptor (G_q) on the cell surface and activates phospholipase C, which is located on the plasma membrane. The lipase hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) into two second messengers: inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 binds with the IP3 receptor in the membrane of the smooth endoplasmic reticulum and mitochondria to open Ca^{2+} channels. DAG helps activate protein kinase C (PKC), which phosphorylates many other proteins, changing their catalytic activities, leading to cellular responses.

Ans.3. <u>Factors affecting drug action-</u>

The specific effect which drugs exert on certain organs may be altered in both intensity and rate of appearance and disappearance. This variance of drug action may be due to a number of factors not inherent in the drug itself. This chapter, therefore, deals with the following factors which modify drug action: route of administration, rate and degree of absorption, rate of elimination, effect of other drugs, tolerance, idiosyncrasy and allergy, disease.

- Age Factors.
- Body Weight.
- Child.
- Drug Interactions.
- Drug Tolerance.
- Genetics, Medical.
- Pharmaceutical Preparations/administration & dosage.
- Pharmaceutical Preparations/metabolism.

Ans.4. <u>Absorption-</u>

In pharmacology (and more specifically pharmacokinetics), absorption is the movement of a drug from the site of administration to bloodstream.

Absorption involves several phases. First, the drug needs to be introduced via some route of administration (oral, topical-dermal, *etc*.) and in a specific dosage form such as a tablet, capsule, solution and so on. Absorption depends upon the route of administration.

In other situations, such as intravenous therapy, intramuscular injection, enteral nutrition and others, absorption is even more straightforward and there is less variability in absorption and bioavailability is often near 100%. It is considered that intravascular administration (e.g. IV) does not involve absorption, and there is no loss of drug. The fastest route of absorption is inhalation, and not as mistakenly considered the intravenous administration.

Absorption is a primary focus in drug development and medicinal chemistry, since the drug must be absorbed before any medicinal effects can take place. Moreover, the drug's pharmacokinetic profile can be easily and significantly changed by adjusting factors that affect absorption.

- Lipid water solubility. Lipid water solubility coefficient is the ratio of dissolution of **drug** in lipid as compared to water
- Molecular size. Smaller the molecular size of the **drug**, rapid is the **absorption**
- Particle size
- Degree of Ionization
- Physical Forms
- Chemical Nature
- Dosage Forms
- Formulation

Ans.5.

a) cAMP signal pathway-

The cAMP signal transduction contains 5 main characters: stimulative hormone receptor (Rs) or inhibitory hormone receptor (Ri); stimulative regulative G-protein (Gs) or inhibitory regulative G-protein (Gi); adenylyl cyclase; protein kinase A (PKA); and cAMP phosphodiesterase.

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b) Phosphatidylinositol signal pathway-

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Ans.6.

a) <u>Drug Metabolism and renal Excretion-</u>

The liver is a major site for drug metabolism. The goal of metabolism is to produce metabolites that are polar or charged, and can be eliminated by the kidney. Lipid-soluble agents are metabolized by the liver using two general sets of reactions, called phase I and phase II.

Phase I reactions frequently involve the P-450 system. Phase II reactions are conjugations, mostly with glucuronide.

Phase I reactions convert lipophilic molecules into more polar molecules by introducing or unmasking a polar functional group, such as an —OH or —NH_2. Most of these reactions utilize the microsomal P-450 enzymes. Phase I reactions are the basis of a number of drug interactions. There are a whole series of cytochrome P-450 enzymes that can be inhibited or induced. Of these, CYP3A4 plays a role in the metabolism of about 50% of the drugs that are currently prescribed. Inhibition or induction of CYP3A4 by one drug will affect the levels of any other drug that is also metabolized by CYP3A4. For example, rifampin induces CYP3A4 that can increase metabolism of estrogen, thus reducing the effectiveness of birth control pills. Some textbooks include lists of drugs that inhibit or induce CYP3A4. Don't try to memorize these lists. Be aware of the potential problem and learn the most commonly interacting drugs as you gain experience. There are also known genetic variations in levels of CYP450 enzymes. Phase II reactions are conjugation reactions. These combine a glucuronic acid, sulfuric acid, acetic acid, or an amino acid with the drug molecule to make it more polar. The highly polar drugs can then be excreted by the kidney.

Renal elimination of drugs involves three physiological processes: glomerular filtration, proximal tubular secretion, and distal tubular reabsorption.

1. *Glomerular filtration:* Free drug flows out of the body and into the urine-to-be as part of the glomerular filtrate. The size of the molecule is the only limiting factor at this step.
2. *Proximal tubular secretion:* Some drugs are actively secreted into the proximal tubule.
3. *Distal tubular reabsorption:* Uncharged drugs may diffuse out of the kidney and escape elimination. Manipulating the pH of the urine may alter this process by changing the

ionization of the weak acids and bases. This process was described in Chapter 3 in the context of passive diffusion of drugs across membranes. However, for a drug to be excreted, it needs to be charged so that it is trapped in the urine and can't cross the membrane to sneak back into the body.

b) Drug Distribution-

Drug distribution refers to the movement of a drug to and from the blood and various tissues of the body (for example, fat, muscle, and brain tissue) and the relative proportions of drug in the tissues.

After a drug is absorbed into the bloodstream, it rapidly circulates through the body. The average circulation time of blood is 1 minute. As the blood recirculates, the drug moves from the bloodstream into the body's tissues.

Once absorbed, most drugs do not spread evenly throughout the body. Drugs that dissolve in water (water-soluble drugs), such as the antihypertensive drug atenolol, tend to stay within the blood and the fluid that surrounds cells (interstitial space). Drugs that dissolve in fat (fat-soluble drugs), such as the antianxiety drug clorazepate, tend to concentrate in fatty tissues. Other drugs concentrate mainly in only one small part of the body (for example, iodine concentrates mainly in the thyroid gland) because the tissues there have a special attraction for (affinity) and ability to retain that drug.

Drugs penetrate different tissues at different speeds, depending on the drug's ability to cross membranes. For example, the antibiotic rifampin, a highly fat-soluble drug, rapidly enters the brain, but the antibiotic penicillin, a water-soluble drug, does not. In general, fat-soluble drugs can cross cell membranes more quickly than water-soluble drugs can. For some drugs, transport mechanisms aid movement into or out of the tissues.