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THE CHEMISTRY BETWEEN PHARMACOLOGY AND CHEMISTRY

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ABSTRACT:
In this super specialization era, scientists have differentiated themselves in different classes like Chemists, Pharmacologists and Biologists etc. In the initial part of our studies, we have divided the science into many branches or streams. As we go to higher studies at research level, we have found that there is merging of branches or streams that we had divided initially. Various branches or streams are inter-dependent. Let us see the interesting interdependence or the chemistry between Pharmacology and Chemistry.

INTRODUCTION:

This is an era of super- super micro specialization. We have divided the studies in three basic streams - science, arts (humanities) and commerce. The branch of science is further divided into three sub divisions – biology, chemistry and physics. Every student wants to be a specialist in it's branch. A Chemistry student wants to concentrate on chemistry subject and proudly called himself or herself as Chemist. Similarly a student who has done specialization in Pharmacology, called himself or herself as Pharmacologist. In pursuing higher studies, the students concentrate on their subject and ignore other subjects completely. They have to pay the price for this willful ignorance. As we go to higher studies at research level, we have found that there is merging of branches or streams that we had divided initially. Various branches or streams are inter-dependent. Let us see the interesting inter-dependence or the chemistry between Pharmacology and Chemistry.

Chemistry is defined as branch of science in which we study chemicals or medicines, their structure at atomic and molecular level or compound level. In chemistry we study various properties (formation, decomposition, analysis, storage, actions and transformations) of an element or compound and study it's physical, chemical, organic, inorganic, stereochemistry and other properties.

Pharmacology is a branch of science in which we study drugs. A drug is defined as the chemical which is used for diagnosis, prophylaxis, prevention and therapeutic treatment of a disease or disorder so as to maintain physical or mental well being of a person. In pharmacology, various aspects of drugs are studied like, Pharmacokinetics, Pharmacodynamics, Adverse Drug Reactions, Toxicological studies, drug-drug

interactions. Pharmacokinetics deal with ADME i.e. Absorption, Distribution, Metabolism and Excretion of the drug molecule in our body. Pharmacodynamics deal with mechanism of drug action. Adverse Drug Reactions is the undesired actions of drugs on human body. Toxicological studies deal with the study of toxic or lethal effects of drug. In toxicology study we study the LD50 and ED50. LD50 is the lethal dose level at which the drug shows lethal effect in 50% population and ED50 is the effective dose level at which the drug shows therapeutic effect in 50% population. In drug-drug interactions, the reactions between two or more drugs are studied. The drug-drug interaction may be chemical reaction, potentiating actions or inhibitory actions.

No drug molecule is perfect. Every drug molecule or drug moiety has certain limitations in its therapeutic effect, be it is in terms of spectrum, resistance or side effects. So there is always scope of discovery of new drug molecule.

In drug discovery or research, initially derivatives or analogues of an established drug moiety are synthesized. Derivatives or analogues are the established therapeutically active and effective drug molecule or moiety, attached with different functional groups. The criteria of selection of various functional groups depend on the requirement of the researcher, whether the additional feature required in new derivative is additional spectrum, solution of resistance, increased distribution in body tissues, or brain, increased bioavailability, increased lipophilicity/ hydrophilicity or vice versa, decreased side effects like, acidity, g.i. side effects, taste masking, central side effects like nausea, vomiting, giddiness, or to take care of hepatotoxicity or nephrotoxicity. There are a large number of reasons for development of a new drug derivative. Discovery of totally new molecule is very difficult. Most of the researches in pharmacology or chemistry are involving the extension or reduction in the functional groups of the existing drug moiety.

A large number of derivatives were synthesized in the chemistry laboratory. It require a long time. Months were required for this step. After these derivatives were synthesized, then comes the important step of checking the pharmacological activity or therapeutic efficacy of these new drug derivatives. The therapeutic or pharmacological effect of new derivatives is checked on various primates and non-primate animals. This requires permission from Animal Ethical Committee under the guidance of guidelines laid down by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). This again takes time. Then availability of required animals is another time consuming parameter. Then comes the actual experimental work on animals. This again consumes time. Then comes the interpretation of results or findings.

In the beginning of research the big question is selection of drug and its site of action. Here comes the helping hand of chemistry which helps the pharmacologists in above action. Now let us discuss how Pharmacology and Chemistry are interlinked:

Chemical Basis of Pharmacokinetics:

1. **Receptors and Isomers :** Normally the receptors involved decides the selection of site of drug action and vice versa. Chemically speaking a drug moiety may have two isomers- the dextrorotatory and levorotatory. Accordingly the drug receptors are stereospecific i.e. either dextrorotatory form of drug molecule or levorotatory form of isomer fits into specific receptor. The active form of drug is decided by this factor of fitting the receptor. Generally one form of drug i.e. dextrorotatory or levorotatory form is the active form. But sometimes both the forms are active or sometimes the separation of these isomers is too expensive that a mixture of both isomers is considered as active drug.

2. **Chemical Nature of Drug :** (Protein/ Carbohydrate/ Fats or lipids or oils) As most of the receptors are proteinous in nature, so nature of drug decides the rationale of action of drugs. The chemical structure of layer responsible for absorption also becomes one of the decisive factors for drug action. Normally the skin is the layer of absorption. It is a layer of phospholipids. So, lipid or oil based drugs have a better absorption.
3. **Ionization of Drug Molecule:** Generally a chemical or drug molecule occurs in two forms- ionized form and non-ionized form. The drug which is in unionized form has a better drug action as unionized drugs are better absorbed. The dissociation of a drug molecule depends on pH of the media i.e. an acidic drug molecule remains in unionized form in stomach, where pH is acidic. However a basic drug molecule remains in ionized form in stomach's acidic pH. So, basic or alkaline drug is very less absorbed in stomach. Similarly a basic or alkaline drug remains in unionized form in intestine where pH is alkaline or basic. Hence basic or alkaline drug has a better absorption in intestine and show a better drug action. However an acidic drug remains in ionized form in intestine and hence poor absorption and hence poor drug action. The dissociation of a drug molecule is guided by pKa, the dissociation constant.
4. **Hydrophilic / Hydrophobic Character:** A hydrophilic drug is soluble in water. So the absorption of drug is affected by this factor. Hydrophobic drug is water hating or water insoluble drug. This factor also influences the drug absorption and hence it's action.
5. **Lipophilicity Character:** Lipophilic means lipid loving or lipid soluble drug. As the skin, the absorbing layer is made up of phospholipids, so lipophilic drugs have more absorption and hence better drug action.
6. **Bioavailability of Drug:** Bioavailability of a drug is the amount of drug that finally reaches in the blood or plasma. Above listed factors influence the bioavailability of drugs. Normally more bioavailability means a drug is more potent and hence better spectrum and better therapeutic action.
7. **Half-Life of Drug** ($t_{1/2}$): Half-life of a drug is the time duration in which the amount of drug in blood plasma reduces to half of its maximum concentration. Half life is also influenced by metabolism or excretion of drug from blood. Half life helps in deciding the dosage frequency of the drug.
8. **Distribution of Drug:** Distribution of drug in body is decided by the chemical nature of drug molecule. The knowledge of chemical nature of drug molecule helps in understanding the distribution of drug molecule in human body, whether it reaches the body tissues, crosses placenta, blood brain barrier, synovial fluid, in gums, soft tissues, liver, kidney, lungs, heart etc. the vital organs of the body. The hydrophilicity, lipophilicity nature becomes the deciding trait in distribution of drug, in human body.
9. **Metabolism of Drug:** The metabolism of a drug is a chemical reaction by which most of the drugs or parts of them are converted into inactive, inert form. Sometimes few drugs (known as Prodrugs) are converted into active form. Metabolism involves various chemical reactions like oxidation, reduction, cyclization, decyclization, conjugation, hydroxylation, methylation etc. So understanding metabolism requires clarity in basic knowledge of chemistry. Most of times, metabolism of drugs occur in liver. Few drugs may be metabolized in kidney. Whenever we take a drug orally, it is absorbed from intestine and reaches in liver where metabolism took place. This is known as first pass metabolism. Then this metabolized drug is circulated in entire body.

Few drugs, when administered through sub-lingual or parenteral route bypass this first pass metabolism.

10. **Excretion of Drug:** Again chemistry helps in understanding excretion of drug from our body. The drugs are normally excreted in urine. Some drugs may be excreted in faeces, saliva, mother's milk, through lungs via exhaled air. In understanding excretion of drugs, clearance is an important term. Clearance of a drug is the removal of the drug from a volume of plasma in a unit time. The process of clearance involves various complicated chemical reactions like isotonicity, hypertonic or hypotonic, ionized or unionized form of drug, dissociation constant, acidic or basic nature of drug. By altering the acidic pH of urine, the antibacterial activity of an antibiotic used in treating urinary tract infection can be increased.

(A) **Chemical Basis of Pharmacodynamics:** Pharmacodynamics deals with mechanism of drug action or how a drug moiety shows its action. To understand this, we have to understand how a drug molecule shows its therapeutic action. The drug may show its action via ion channels like sodium channel, potassium channels, calcium channels, chloride channels. Sodium channels normally deal with the excitatory action or hyper secretion. Chloride channels deal with the inhibitory action or hyposecretion. Calcium channels deal with the contraction of muscles. Various enzymes like Sodium/ Potassium Adenosine Triphosphatase (Na^+/K^+ATPase), Hydrogen/Potassium Adenosine Triphosphatase (H^+/K^+ATPase) enzymes, cyclooxygenase enzymes plays important role in understanding the mechanism of drug action. Certain drugs show their action via G-protein coupled receptors (GPCRs).

(B) **Recent Trends:** Previously researchers began with drug derivatives/moieties and search for suitable targets in terms of receptors. Recently the new trends allow the process in reverse way i.e. first the target receptor is selected and then a suitable drug moiety or it's derivative is selected. Recent developments in chemistry in terms of QSAR (Quantitative Structure Activity Relationship) techniques help in preparing a list of suitable derivatives. This technique saved a lot of time in preparation of derivatives and testing the pharmacological action. This technique suggests various alternatives on the basis of chemical structure and properties of the original drug molecule or moiety. These alternatives are further studied for shortlisting the most potent drug derivatives. Here the chances of success in getting effective or therapeutically active drug molecule have increased manifolds or chances of failure decreased to a greater extent.

This , in short, saves time, money, infrastructure, animals etc. in discovering new drug molecules or derivatives.

(C) **Future Challenges:** The researcher should have a sound base of both chemistry and pharmacology for meeting future challenges. Till date, whatever researchers have achieved, are only a drop in the ocean. Still more clarity is required in understanding the drug action, chemical composition of human body, enzymes, tissues at microcellular level. Moreover clarity is sought regarding the therapeutic effect and side effects / adverse effects of drugs. We have to minimize the drug testing on animals as we have to minimize the cruelty to animals. We have to reach to that level when we have sufficient data bank to recapitulate all the chemical properties and pharmacological actions of any or all the products available on earth. In the last, but not the least we have to develop drugs without any adverse drug effect.

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