**Organic Chemistry In Biology And Drug Development**
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**Lecture - 41**
**Introduction to Drug Discovery Process**

Welcome to this course called 'Organic Chemistry in Drug in Biology and Drug Development'; So far, in the first part of this course, we have discussed the application of organic chemistry in biology. And we have now the perfect background to go into the second topic that is the drug development process and the role of organic chemistry, how does it help. Now before we go on to the actual organic chemistry we need to know certain aspects of this drug discovery process.

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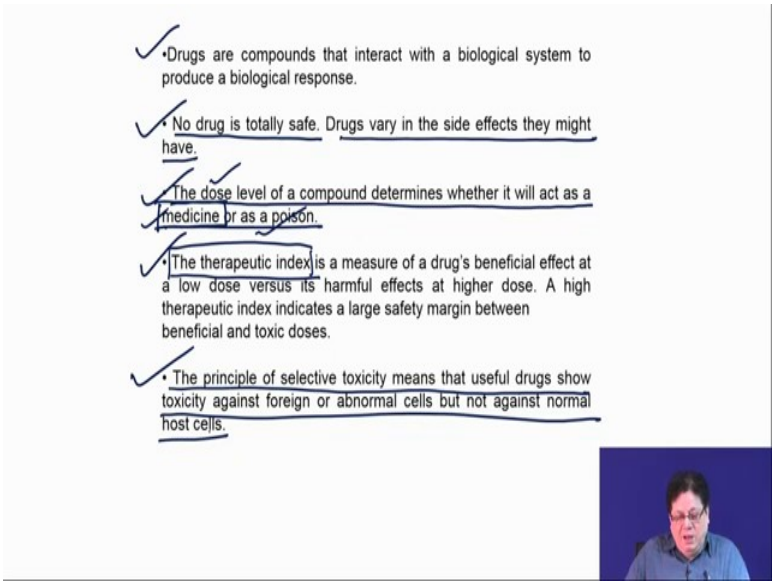


First of all what are drugs? And then what is the safety margin on all chemicals which has some effect on the body? Whether all are drugs or not? So, I think some preliminary knowledge is required before we move on to the actual drug design and discovery process.

Now, drugs are basically compounds that interact with a biological system to produce a biological response. So, basically if you have a living system and you take a chemical and that chemical goes inside and produces some affect that is called the biological response. Now the question is that how safe are these chemicals, which produce some

biological effect? So, this definition basically includes any chemical which produces some biological effect. Now that biological effect may be a toxic effect, may be having a lethal action on the living system or may be having a beneficial effect.

The drugs should be such chemicals which have beneficial effect on a living system like the human as we will consider the human as our model. Now no drug is totally safe, most of us know that the all drugs have some side effects and the quality of drug varies according to the side effects that they might have.

Now to minimize the side effect and to maximize the biological response, we need to adjust the dose level. What is called the dose? Like some pills are taken in 500 milligram and maybe the restriction is that you can go up to 4 times a day, some could be 2 times a day. Now how was this dose determined? That is determined by the beneficial effect *vis a vis* the toxic effect that it may have. So, if you cross certain dose, the same drug may act as a poison, it can produce a toxic effect or sometimes a lethal effect that a person may die of that.

So, dose is very important and no drug is totally safe. Now, this dose development dealing with how to maintain the proper dose is very important, because as I told you that a drug can be a medicine or it can be a poison. The therapeutic index is a parameter which tells you how safe is the drug; that means, suppose if you found that 500 milligrams of dose is sufficient to produce a beneficial effect and suppose you cross 10 gram, a 10 gram dose causes a toxic effect. So; that means, you have a therapeutic window that 500 milligram is a beneficial effect and 10 gram is a toxic effect. So, in between you do not have any problem. So, you can take 500, even you can take 1 gram, so long as you are below the toxic dose, so that is beneficial to the person or to the human.

Now if this window is very small, the beneficial effect and the toxic effect then there is a problem. And you know the term ‘drugs’ has been a misnomer in today’s context, because we are hearing drug addiction and then drug poisoning etc.

So, basically we are talking about drugs which are having beneficial effect and that can be regarded as the medicine. So, the drugs which are having beneficial effect are called medicines; so all drugs are not medicines. The drugs that we talk about in relation to addiction are the ones that basically create some kind of addiction, so that the person

takes the drug even if he or she does not require that. But his mentality is such that he thinks that taking that particular chemical as a drug will cure whatever problem he is having.

We have heard of many cases of death due to drug poisoning and that is because these people cross the therapeutic index of whatever is prescribed to have a beneficial effect. So, once they cross the therapeutic index, or the toxic dose, they are going to have these toxicity related deaths.

Now it is very interesting that the human body is made up of a very complex biological system. So, what will happen, now if you take a chemical; obviously, they are going to interact with this complex system which is going to affect the chemistry or biochemistry that is going on in the body; that means perturb the metabolism of the body.

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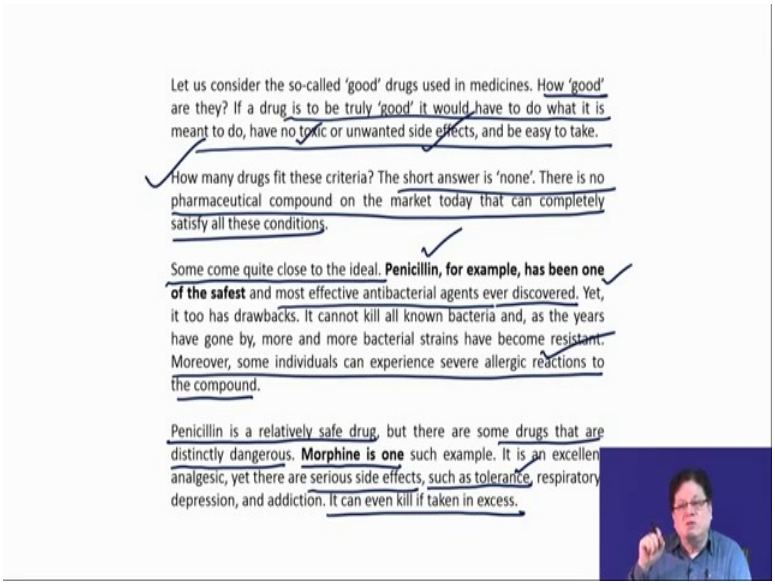


Now, if this complex processes are all being targeted or are being disturbed by this external agent which is called the drug; then that is not a very safe drug or that is not a very specific drug. If a chemical interacts with several biochemical agents or biochemical processes inside a living organism then it is not a good drug. Now that means, a good drug is one which basically targets specifically some of the biological agent that is present inside the body; it could be a protein, it could be nucleic acid, it could be carbohydrate or lipid without causing any toxic or unwanted side effect.

But as I told you, there is no drug in the market that completely satisfies this condition; that means, that only targets one particular molecule inside the body without having any toxic or other side effects. Now side effects come from interaction of this chemical or this so called drug with other molecules which are not targeted in principle. Suppose I have some cholesterol related disease, like hyper cholesterol, the cholesterol is higher then what is expected in the normal human being.

Now if cholesterol is very high; that means, the cholesterol is made in the body at a much at a higher level, then what is required. Now who makes the cholesterol? It is the enzymes that are present in the body. So, suppose I target one of the enzymes which are involved in the biosynthesis of cholesterol.

So, if I inhibit that enzyme, then the cholesterol biosynthesis will stop or it will be modulated, depending on the type of inhibition and the $IC_{50}$ values of the inhibitor. But if that inhibitor which is supposed to reduce the cholesterol level, interacts with some other liver enzymes which are essential for metabolism of many of the chemicals or it is targeting other enzymes which are involved in the metabolism of the diet, then what will happen? Then I have the side effect or this chemical produces acidity inside the stomach like what aspirin does.

Then that is not a good drug. More the side effect; that means, more the interaction with other chemicals inside the body, other than the target, then you have these toxic effects arising from the drug. But just to be very clear that no chemical and no drug or no medicine in the pharmaceutical market today completely satisfies all these condition: it should not have any side effect, no toxic effect and that its therapeutic window should be very high.

But some drugs come very close to these ideal drugs; one example is penicillin. Penicillin has been one of the safest and most effective anti-bacterial agent ever discovered. It does not have toxicity or side effect; that means, it is not targeting other enzymes or nucleic acids or any other biological molecule which is essential for the human being. It is targeting only the bacteria that are causing the disease and when we discuss the mechanism and action of penicillin you will know why it is so specific and why it is so effective and why it does not have side effects.

However, it still has got some problem like many of the individuals can experience severe allergic reactions to this compound. So, whenever you go to the doctor and if he is prescribing penicillin, the first thing he will ask is that are you allergic to sulphur; because penicillin has a sulphur moiety. If the patient is allergic then the doctor will not prescribe any penicillin type of molecules; under such situation, the other types of antibacterial agents have to be prescribed.

Thus penicillin is relatively safe, because if you do not have allergic reactions then it does not have much other side effects. There are some of the drugs that are distinctly dangerous. Morphine is one such example. Morphine is a natural product and that is used as an analgesic; that means, pain reliever and it is given mostly to terminally ill patients suffering from cancer, because the pain is too much and at that time one has to take morphine.

However the problem is, it has got side effects and one of them is what is called tolerance; that means, may be today 500 milligram of morphine is sufficient to give me relief from the pain, but after one month 500 milligram may not be sufficient, I have to increase the dose. The same thing happens with many of the sleeping tablets; that you start with a very low dose, but as days pass by, the dose has to be increased. Now this is what is called tolerance; that means, if the body develops tolerance very quickly; consequently the morphine dose has to be increased.

And so, basically you run the risk of crossing the lethal dose (the dose that is required to kill the person) and sometimes that may even happen. Similar is the case heroin, which is another derivative of morphine that is also a very good pain reliever, but it is not prescribed. And these drugs are only available on prescription; it is not to be used by anybody without any prescription because of this addiction problem and the problem of tolerance.

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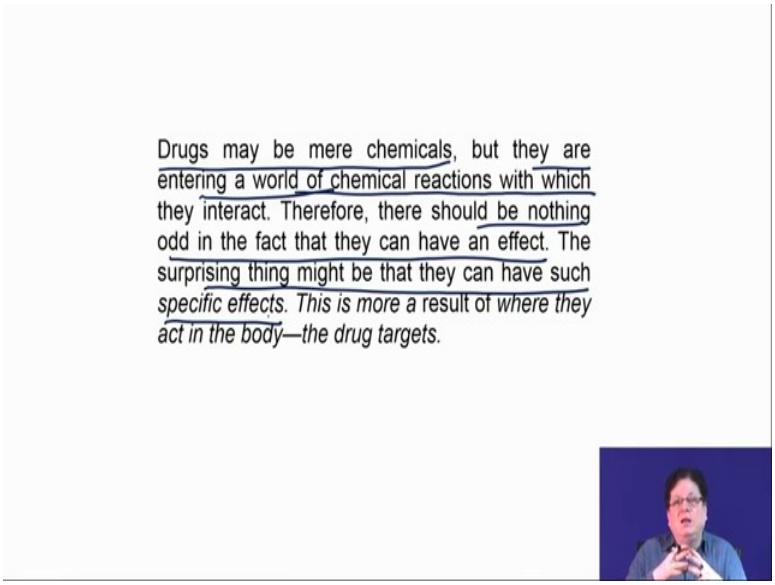


Now, the next question is what are drugs? I already told that drugs are mere chemicals, but they are entering a world of chemical reactions; that means, they are entering a biological system which is called a biological world and with which it will interact. Therefore, there should be nothing odd in the fact that they can have an effect. However, the surprising thing is that they can have specific effects.

These chemicals that can be branded as drugs only have some specific effects; that means it mostly interacts with something which is the causative agent of the disease, but without interacting with others. But as I told you, side effects are there, but the medicinal chemist or the persons who are associated with drug discovering process, try to minimize the side effect while maximize the efficacy of the molecule.

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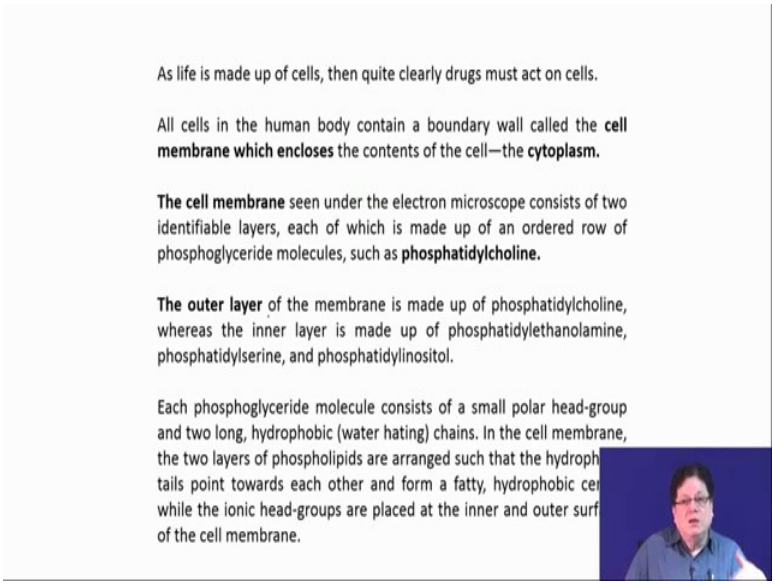


Efficacy means that efficacy towards relief of the disease.

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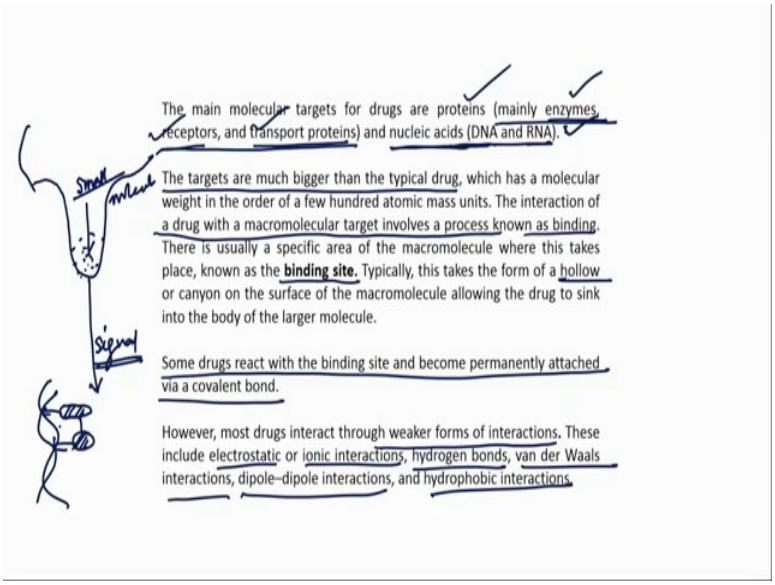


Now, the question is that what are these targets? The targets could be proteins. Now proteins can be enzymes, so you can target enzymes, you can target receptors; receptors are basically proteins which are on the surface of a cell and when a small molecule binds and then it produces some effect and which is very important.

And so, some may be over active receptors, so you have to make a molecule which goes and binds and stop the signaling path way or reduce the extent of signaling pathway. And

some could be transport proteins; that means proteins which transport molecules inside the cell. So, if you want to lower the metabolic activity, then you have to target these transport proteins; because transport proteins are basically taking important molecules from outside and taking it into the cell. So, for many diseases, that is needed to be stopped. So, these are the proteins; that means they are mainly enzymes, receptors, transport proteins. Other possible targets can be the nucleic acids (DNA and RNA).

Now nucleic acids are targets mainly when you want to kill the cell by a molecule which goes and destroys the nucleic acid. And this is typically what is required in case of treatment of diseases like cancer, because there you want to destroy the the cancerous cell. Most of the drugs that are based on nucleic acids, but not all, are either anti-cancer agents, anti-viral agents, or they could target other degenerative processes, that are involved. But again, just nucleic acids are mostly targeted in case of cancer; and for other diseases we generally target the proteins and among the proteins I said enzymes, receptors and transport proteins.

One interesting point is that the drugs we take are really small molecules. On the other hand, they are interacting with molecules which are very big, like these proteins which are much bigger as compared to the small molecule that we use as a drug. I am sure you have never noticed a drug which has got a molecular of say 10000, it is always a small molecule and this small molecule interacts with a very large molecule.

We have gone through the enzyme chemistry; that the enzyme also take some small molecule and converts into products and there the molecules are very small and they go and bind to what is called an active site. Now the small molecules, after binding to the enzymatic site, they undergo some transformation.

Now, there are proteins which has got a binding site, but there is no as such chemical reaction; but as the small molecule binds, it creates a disturbance on the enzyme and that disturbance creates a change in conformation and the change in conformation creates a signal and that signal is then transmitted into the cell or other cells and then other biochemical processes which are very important for the survival of the cell that happens.

So, basically we can say that usually the targets are macromolecular targets; proteins or nucleic acids. And usually they have a binding site, especially if they are proteins; they have a site which is called a binding site. And we know what is the active sites. So, the

small molecule goes here and binds. And then creates either, if it is an enzyme then the small molecule is transformed into a product or some other metabolite and if this protein is not an enzyme, but a receptor then the small molecule binds and creates some signal down inside the cell; that means, the cell cytosol.

So, other molecules are told about this binding of the small molecules and then according to that they have to act. Until the small molecule binds there is no such signal. So, this is very important in many of these metabolic processes; this is what happens that a receptor is there and other small molecules binds to the receptor.

In DNA also, if you want to design an anticancer agent, then you have to design a molecule which destroys or breaks the DNA molecule. But to make it very specific, it should have some binding partner; the smaller molecule should have some binding partner which allows it to sit onto to or to interact with the DNA and not with other macromolecules.

So, basically if you have a DNA molecule, and if you have a small molecule here and you want it to be very specific to the DNA, then you need to attach something which binds to the DNA and this goes and cuts the DNA or destroys the DNA. So, selective binding is always important in drug discovery.

Now the question is, what are these binding interactions? It is very similar to the enzyme chemistry; the binding interactions could be many weak interactions like electrostatic, ionic interactions, hydrogen bonds, van der Waals interactions, dipole-dipole interactions, and hydrophobic interactions. On the other hand, there could be some inhibitors or some molecules which goes and binds to the protein and then forms a covalent bond, they are called irreversible systems; the ones binding through non-covalent interactions are the reversible ones.

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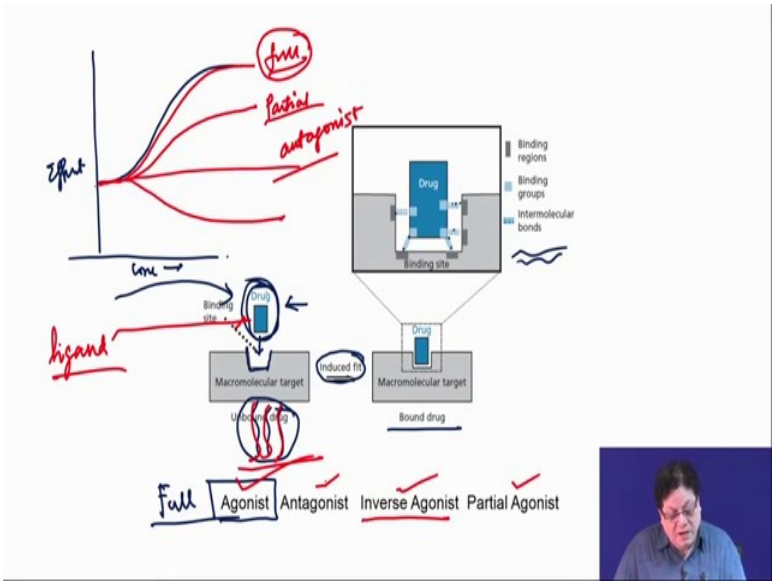


Now, this is the diagram; suppose this is your molecular target and it has got a pocket, that pocket is called the binding site. And now you give a chemical which is a drug, and which is specific for binding to this pocket; so, that goes and binds. So, basically this geometry is complimentary to the binding site; but the binding site may be slightly distorted, it is not totally tailor made that it goes and binds and there is no adjustment on this binding pocket.

Usually what happens; that the binding pocket is very close to the geometry of the drug, but as it goes, it changes the conformation a little bit, so as to adjust the drug for sitting properly at the binding site; this is what is called induced fit. You can see that this is slightly slanted; this binding site is still little bit wider, but as it binds and so these two white portions they close the gap between this end and that end, so that the drug sits in the binding site properly.

Now this is the enlarged picture and we now have all these weak interactions, because this drug will go not only because of the geometric complimentarily, there must be some other electronic forces like the weak interactions. Now as soon it binds, if it is a receptor then you have the generation of signals that we know.

Suppose I have a receptor which has a natural metabolite as the substrate and when it sits into the active site then it develops all these signals and these signals are transmitted by a process call signal transduction and that creates lot of ion movements, channel openings.

Basically it starts a cascade of reactions involving several metabolic pathways; but those metabolic pathways are very important.

A very simple example, if I take a neurotransmitter, say dopamine; so dopamine will have a binding site on the receptor, so, dopamine must be having some receptor. And when the dopamine sits onto the binding pocket, it creates a signal and the overall effect we know that it creates something which elevates your mood. Now if somebody is very depressed, that means, his dopamine level has a problem, the concentration of dopamine has a problem.

He cannot produce dopamine because it is inbuilt in his metabolic system. So, what you have to do, you have to give a molecule from outside which looks like dopamine. So, in addition to dopamine you have another molecule which when sits onto this binding pocket or binds to this site it also creates the same signals. So, based on this principle that the drug goes into the binding pocket and creates a signal, we are talking about the receptor chemistry, we are not talking of any chemical reaction.

So, here there are several things that can happen; I can make a molecule which also like the natural metabolite dopamine goes and binds and gives similar kind of signal that is called an agonist. An agonist is a molecule which goes into the active site, interacts with the binding site like the natural metabolite and produces the same kind of signal. Now, a question that arises is that what is the extent? What is the strength of this signal? Because sometimes the strength of the signal may be very high, like the original metabolite, sometimes the signal may be little less. Accordingly, you have full agonist and partial agonist.

What is a full agonist? That means if I have a graph like this, suppose the effect is something like this, this is a positive effect. If it is for a natural ligand, I plot its activity versus concentration. This is first the natural curve; that means, I do not have the drug, I add the small molecule like dopamine, the natural metabolite and I see what is the response, what is the effect suppose this is the curve and then I replace this natural metabolite and add the foreign molecule as the drug.

And suppose it produces similar kind of effect, so, it is a full agonist. But if it produces a partial effect like this at similar concentration, then it is a partial agonist; but there are some molecules which goes and sits into the binding site and does not produce any

effect; that means, it does not produce any effect. So, the natural metabolite needs more concentration. So, more concentration to stop the external molecule from binding, it is like your competitive inhibition.

Suppose you have a very active dopamine level. So, you need to calm down, you have to now use some molecules with sits at the active site, so that the drug cannot bind at this pocket and it does not produce any signal for signal transduction. Thus when the foreign molecule sits here, basically it stops the metabolic process that you are interested in, so that will be called an antagonist.

So, an antagonist basically goes and binds and does not produce any signal. Partial agonist produces partial signal like the original metabolite which generally we call a ligand, because this is nothing but a ligand and the macromolecule that interaction we are talking about. Thus there are some molecules which produces similar effect like the natural ligand and then there are some which actually produce opposite effect and that is called inverse agonist.

Now, what is this opposite effect? Let us consider some excitory neurotransmitters; that means, they excite the system. But, suppose the molecule that you are adding is now acting as an inhibitory neurotransmitter like system; that means you are targeting an excitory neurotransmitter and you are inhibiting the effect of that excitory neurotransmitter. So, that is an opposite effect; so if you have inhibited it; suppose it is an excitory neurotransmitter that is having this type of curve and if you have a molecule which produces a inhibitory curve like this, then that is called inverse agonist. So, these molecules, these terminologies are very important in drug design and then agonists have full and partial.

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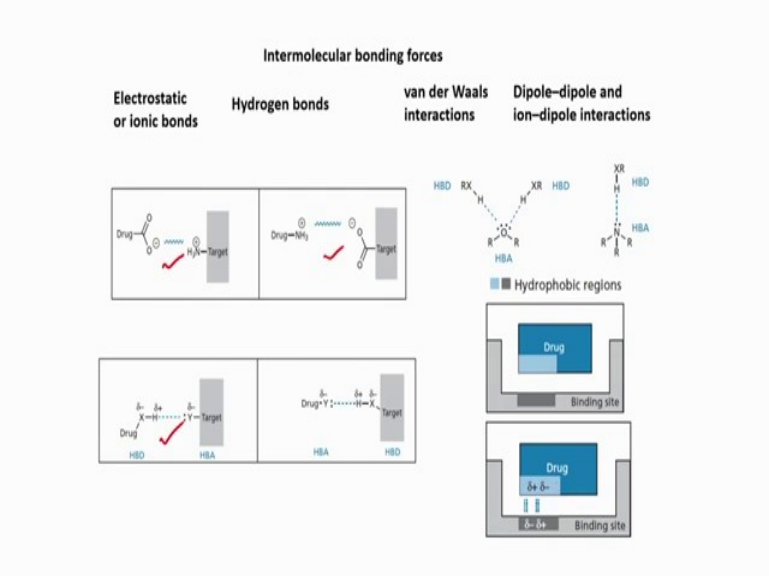


These are the some of the interactions, I think this is already known that this is the electrostatic interactions and this is the hydrogen bonds that type of interaction. This drug could be a donor, this receptor could be an acceptor, or drug could be acceptor and this receptor could be donor. And hydrophobic interaction implies that there are lots of hydrophobic amino acids residues here, and the drug also has lot of hydrophobic portions in it. So, that can induce these hydrophobic interactions.

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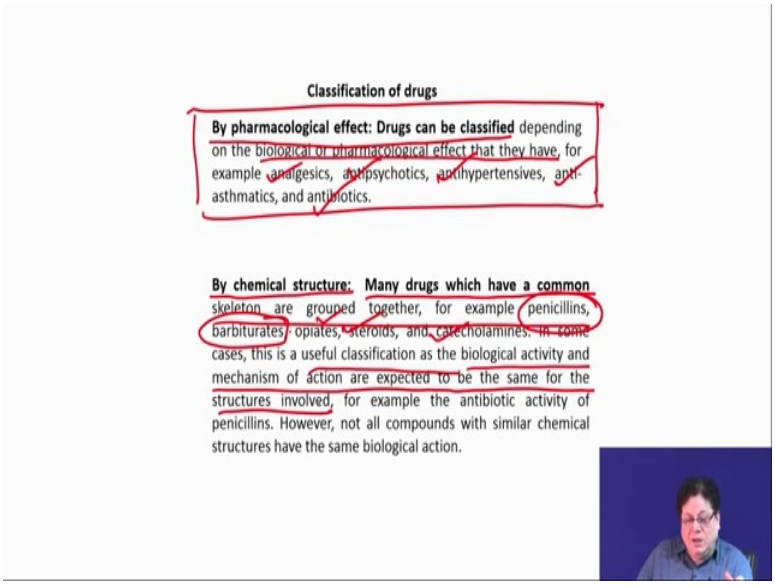

How the drugs are classified? Classification of drugs is little difficult. Drugs can be classified, depending on the biological and pharmacological effect that they have, like we can call some drug analgesics that means, pain relievers, some drugs antipsychotics that means, they effect the brain and then the mental condition,. anti-hypertensive that means, they effect the blood pressure or lower the blood pressure, then we have anti-asthmatics so that works against asthma and then you have antibiotics that works against foreign bacteria.

However this does not help an organic chemist, the problem is this does not give you any structural information; like many antibiotics are there which can vary widely in structure. So, this classification is good for the doctors that he has a list of anti-psychotics; he has a list of anti-hypertensive. But as an organic chemist trying to develop new drugs, he or she wants to know what are the structures, what is the similarity between the structural similarities between these classes which are grouped together like a analgesics what are the similarity.

Now we are more interested in the organic skeleton and what it has; like we have now some molecules or some group of drugs that are called penicillins, some are called barbiturates. Barbiturates are also a heterocyclic framework obtained from urea and malonic acid; opiates are obtained from the opium and then steroids, then you have catecholamines. So, that gives the structural pattern; in some cases this is useful classification as the biological activity and mechanism of action expected to be same for the similar structures involved.

So, for organic chemist I will say that this type of classification is more useful to them.

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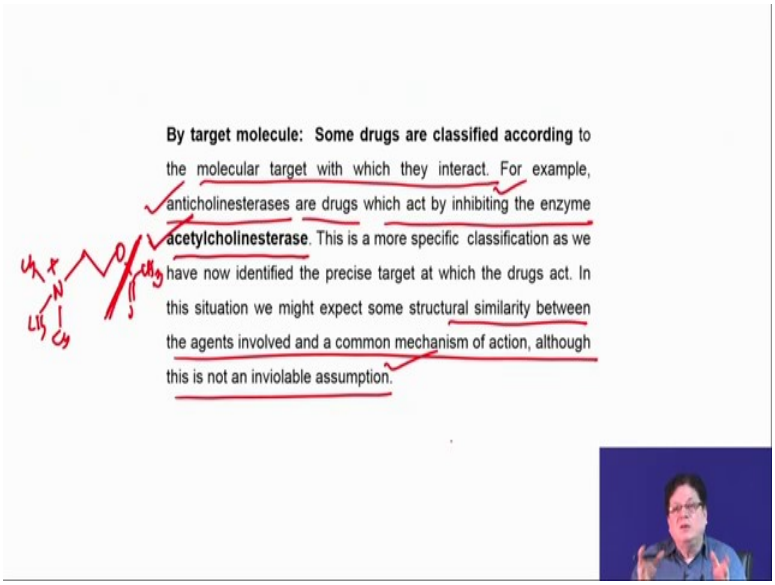


But there are other ways of classifying drugs. So, one was earlier from the biological effect, the second one from structural variation and the third one is according to the target that they interact with. So, I said that every drug has a target. From the target you can classify drugs as anticholinesterases, because acetylcholine is another neurotransmitter. So, if you are developing agonist, antagonist, and inverse-agonist all these against those acetylcholinesterase receptors, so those compounds will be called anticholinesterases.

So, here it is basically inhibiting; there could be two types of anticholinesterase, one is where you can have molecules which interact with the receptor, but another is where there is an enzyme which is acetylecholinesterase which hydrolyzes acetylcholine; acetylcholine is a molecule which is like this. There are three methyls, the nitrogen is plus and then O very simple molecule, but it is a neurotransmitter and it is if you hydrolyze this acetate molecule it becomes it lose it is neurotransmitter activity.

So, if somebody is having low concentration of acetylcholine, that means, its hydrolysis is very fast, you can then inhibit that enzyme which is called acetylcholinesterase inhibition. So, the molecules which actually work on this acetylcholinesterase; acetylcholine remember acetylcholine works by two principle, one is you can control the concentration of acetylcholine or the effect of acetylcholine by targeting the receptor or

by targeting the hydrolysis. Here we are talking about acetylcholinesterase; that means, we are talking about the enzymatic version.

So, if a molecule stops this hydrolysis then those molecules are called acetylcholinesterases, so this is target based. Similarly; however, again target, if you have target based then you might think that only similar molecules go to the same target. So, you can have a notion that all this acetylcholinesterase inhibitors are having very similar structure that may be true, but they are this is not an inviolable assumption, it says that you have to be careful. There are various dimensions of an interaction of a molecule with a target.

Suppose there are 10 possible interactions that a ligand has with the target. Now, some molecules can utilize 5 of these, another molecule utilizes 5 of the remaining and some molecules may be utilizing all the 10 interactions that are happening. So, you have different structural features in every inhibitor.

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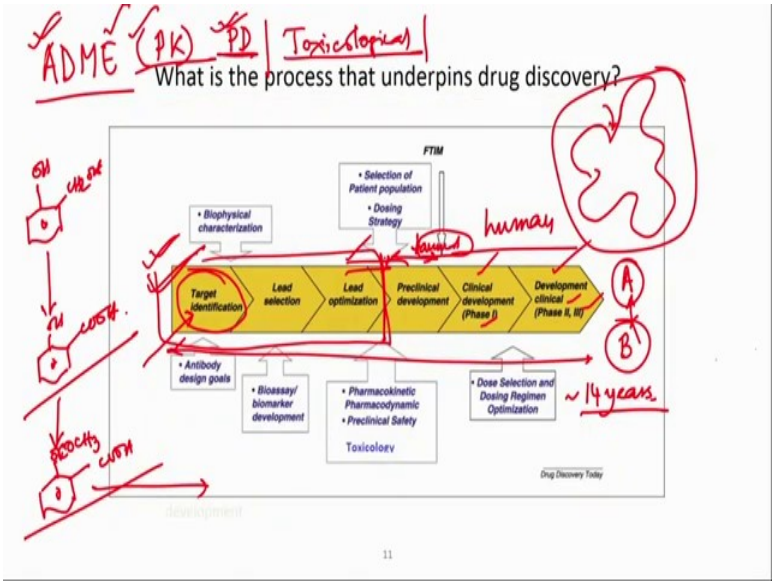


Now, what is the drug discovery process? Let me tell you little bit about that, before we go onto the actual topic. Initially in earlier days, it was kind of what is called serendipitous discovery. Serendipitous discovery means, you are trying to do something and you get something else and that is called serendipity. Like in many cases, some drugs are discovered by looking at nature's signature.

Nature signature means, I will give an example like salicylic acid or acetylsalicylate, which is aspirin; the discovery of aspirin was like this: we all are aware of willow tree with which cricket bats are made, the willow tree grows near the lakes and the ponds. And it may sound very strange, but people those days (we are taking about the 17$^{th}$ century or 18$^{th}$ century) when not much development has happened in chemistry or forget about biology and medicinal chemistry, only looked at the nature.

So, they found that willow trees were growing in a very wet land, as they were very adjacent to the pond or a lake. So, this willow tree must have some resistance against common cold or fever, because we know that if we are drenched in a rain for a particular day and then possibly you will get some fever or headache or all these things can happen. So, it is very strange that people thought that willow tree must be having some compound which is making the willow tree stand upright without having any problem.

So, they were actually connecting the tree with the human being; ultimately what they did, they took the bark and then extracted it, extracted with water and they started to drink this water. And indeed that was reducing the fever and other associated headache etc; but there should be some rational why it is effecting such things. So, some chemist, at Bayer, started looking at the chemical that is there in willow tree and they found that there is a glycoside of salicyl alcohol.

Salicyl alcohol is nothing but this O H. So, it is a glycoside, it is a O-glycoside of salicyl alcohol and then there are intelligent people who immediately thought that this must be the compound, that glycoside must be hydrolyzing and this must be the compound which is the active compound.

And then while doing so, they found that actually this is the one that is called salicylic acid. So, they thought that salicylic acid could be a good chemical which may be acting on the body to have these analgesic activities. But salicylic acid is extremely toxic; you cannot take salicylic acid inside your stomach. What you can do, you can take salicyl alcohol and that goes in the body and then that will be oxidized by enzymes to salicylic acid and then that can show the effect.

So they reduced the acidity of this molecule by blocking it with acetyl group. So, in the body that goes and gets hydrolyzed to salicylic acid and that is why this was giving the anti-analgesic activity. You see these are from signatures of nature; there are many

signatures in and around. So, people were looking at how nature deals with other living organisms, even if it is a plant how are they surviving with the harsh conditions.

One of the classic example of serendipity is penicillin; that Alexander Fleming was looking for something else he was working with lysozyme, but in the process he discovered penicillin. We will discuss that when we cover the antibiotics. Today you cannot wait for some serendipitous discovery to happen or you cannot wait for somebody who looks at the nature and starting gets some idea that we have to do this or do that.

Since the chemistry and biology has advanced so much. So, today's drug discovery is as rational as possible. So, this is the process of today's drug discovery. Suppose somebody is suffering from a disease. So, you have to identify what is the cause of this disease. That means, you have to identify the target, in other words, you have to identify the cause that it is basically causing the disease., For example reason which is associated with high cholesterol level. So, you have the biosynthetic machinery which makes cholesterol that becomes a target.

So, once you have a target, now cholesterol targets are well known, but if it is an unknown disease or if it is a disease where there are many targets possible then if you identify a target, new target today that for cancer this is the target, that this gene is the target, but you have to prove that, that is what is called target validation. If you first identify the target, then you have to prove to the community that yes this is the target and this is the causative agent for this disease.

If it is a gene, what you have to do; you have to make a system where the gene is not present and you show that this is not suffering from the disease. So, you have to do this mutation studies. If it is a protein, you do some engineering studies, either you delete the gene corresponding to the protein and you show that as this protein is not there, so it is not having the disease; so target identification and target validation is the important one.

Then once you have the target, suppose it is a protein then look for what type of protein is this; is it a receptor, is it an enzyme. If it is an enzyme, then try to find out what is the substrate and if the enzyme crystal structure is known, because if it is a protein you can get a crystal structure.

Suppose this is the ultimate shape of the protein and you try to find out what is the active site of the protein. If the crystal structure is known then the problem becomes little bit easier, because then you can design some small molecules and then based on the active site geometry you can design small molecules and see how it is targeting, how it is interacting with the protein. If the protein is not known or if it is crystal structure is not available, then they try to see what is the closest analog of this protein which is available in the crystal that is called homology modeling.

Suppose I have a protein A and the crystal structure of protein B is available. Suppose A has very similar amino acid sequence with B, suppose 70 percent amino acid sequence as similar then we call it has got 70 percent homology. Then as an approximation I can take the structure of B and do my screening of the small molecule. This is nothing but what is also called *in silico* screening; that means, this is you are not making the molecules yet, you have a library of compound you write those structures and then through computational means you try to select this small molecules.

Whatever is giving a very good binding, you select those molecules and then you synthesize them. Now the organic chemist comes into play, you synthesize those molecules and see whether they are really interacting with the target molecule or not. Sometimes, because this computational modeling is still not perfect so, sometimes it happens that out of 10 molecules that you synthesis maybe nothing is interacting very well. So, you have to go back and then make new sets of molecules and then again see whether they interact with your target compound and then if suppose one or two compounds interacted well so, you have to take those molecules, those are the compounds which are called hits.

So, initially the molecules from the library of compounds go through in-silico screening; that means, computational studies and then synthesizing and doing the actual bioassay, whether it is binding to the pocket that of course, now the question is how do you assay that, that how it is binding experimentally. So, that is what is called a bio-assay, an assay system; assay system means which assays the affinity for the external molecule with the, to the target. So, that is another aspect of biochemistry that you have to design an assay, if you do not have an assay you cannot proceed. So, some assay has to be there, which will tell you about the efficiency.

And then so, from hit you again sit together and then there are many tools are there by which you can see the drug like property of the molecule; that means, if the molecular weight is more than 1000, you can immediately say that this is not going to be a drug. Although it is interacting well with the target site; but it cannot be a drug, because for a molecule to be drug and if it is orally taken there are many processes that it has to be absorb properly it should go to the blood stream and then distributed and before the metabolic degradation is happening, it should exert it is effect.

Even if you have a hit, from hit you have to select the leads which is where you basically modify the hit structure and then try to come out with a better one. And once you have the lead selection, then something called lead optimization and for lead optimization you have some tools to optimize the leads, you can use in silico screening; but there are some empirical rules I will tell you. And then once you are through this that I have 10 molecules which have got very good at least in this in-vitro studies; in-vitro means you have the either the receptor or the enzyme and in-vitro means in test tube you are doing all these experiments or in computer, these are in-vitro studies.

And up to that point, you have certain number of molecules in your hand, then what you have to do; you have to do what is called pre-clinical development. Pre-clinical means you have to first study how the drug is absorbed, how the drug is distributed inside the body, how the drug is metabolized in the body and how the drug is excreted from the body, this is what is called ADME studies. But; that means, what the body is doing to the external this drug, the external chemical which is acting as a drug and this is in general that is called pharmacokinetics studies. Pharmacokinetics means, what the body does to the drug and you have another thing which is called pharmacodynamics this means, what the drug does to the body.

So, these studies have to be made, that how the drug is absorbed, how the drug is distributed, how it is metabolized, whether the metabolism is very rapid, then it will not show its activity and then how it is excreted. If it is excreted very rapidly then also it does not serve the purpose, you have to have some optimum concentration of the drug with a sufficient half-life in the blood stream. So, that is called PK, pharmacokinetics studies and there is something which is called pharmacodynamics.

And another important thing is what is called toxicological effects. Toxicological effects means, what are the harmful effects of the drug, is it affecting the kidney, is it affecting the liver, is it affecting the heart. So, these type of toxicological effects also have to be studied. So, once you have satisfactory data here that it is not very toxic, it has got a very good therapeutic window or therapeutic index and then it has good ADME properties and it is also targeting to the intended target that is what falls under the preclinical development.

And after that there is this clinical development; that means, this part involves human, you actually do it on human and this part is partly in-vivo and mainly the animal studies, here you unfortunately have to sacrifice animals here. You have to do these preclinical studies to show the ADME properties and to show the pharmacodynamics properties and to show the toxicological effects. Once they are satisfactory, then only it is given to the humans; but that is also stage by stage process, you cannot give it to the a large number of human population without knowing, because after all animal models are animal models, they cannot really mimic the human body. So, you have to be very careful. So, this is the drug discovery process.

There are clinical phases phase 1, phase 2, phase 3 if time permits we will say what are these phase 1, phase 2, phase 3, but after phase 3 is done then everything, if everything is satisfactory the drug is approved and the time taken from here to there is about 14 years. Thus it is a very expensive and very laborious process. So, only pharmaceutical companies who are very wealthy can invest money and wait for 14 years for a drug to be obtained.

So, I think we will stop here and we will go to the next session and then talk about some of these targets and other related things about drug development.

Thank you.