Medicinal Chemistry
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Lecture No 41
Finding a Lead Part - 1

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Finding a Lead

Welcome back. In the past several lectures we have looked at, you know how drugs are going to be metabolized once they get into the body, how they are administered and you know the various consequences of administering it through various routes and how drugs are excreted.

We have looked at; you know fate of a drug once it is ingested into the body and various aspects of ADME which is basically absorption, distribution, metabolism and excretion.

So in this whole process what we have done is we have started from how, what are the major targets inside the cell to all the way to understanding pretty much how, what happens to a drug once you consume it. And all this process gives us a solid foundation about how to discover a drug.

At this juncture what we look at the various processes by which one finds a lead, Ok. So right at the beginning we discussed this. Drug discovery is nothing but finding a lead compound and so there are various aspects to finding a lead compound. And in today's lecture we will cover some aspects of this, right.

So

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first before we proceed, in order to discover a drug one needs to address a disease, Ok. So we need to choose a disease of our, for which a drug should be discovered.

So, since majority of the drug discovery occurs in pharmaceutical companies, the major question is how does the pharmaceutical company decide which disease to target when designing a new drug.

So this is a really complicated question to answer because what the pharmaceutical company needs to do is to figure out what are the diseases which require new drugs.

And since there are a large number of diseases that affect humans, one needs to make a somewhat of a subjective decision as to why a particular disease needs to be chosen.

The second major aspect of how this choice is made is through economic factors, Ok. So of course you know drug discovery costs a lot of money.

So we need to figure out, you know how to synthesize molecules, how to test them, what kind of testing regimen we want to resort to, and there are many aspects to research and development in pharmaceutical industry which requires substantial amount of financial investment.

So we also need to of course have high quality equipment and we need to be able to train people or be able to get trained personnel to carry out our research and development.

And of course we need a lot of chemicals and biochemicals to be able to do this. So all of this costs lot of money. So economic factors do play a very important role.

So a pharmaceutical company needs to take into account a number of these aspects before choosing a disease.

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So a great deal of research is actually carried out on ailment such as migraine, depression, ulcers, obesity, flu, cancer and cardiovascular disease.

And these are, as you can see, very important diseases obviously. So for example migraine and depression is a major problem in much of the world, and so is cancer.

And of course cardiovascular disease is becoming a huge problem in developing countries as well. But these are driven by the patients that are present in developing nations, Ok.

So a large number of people suffering from these diseases are going to be consumers of the medicine that is developed in advanced countries.

And there are a number of diseases which are highly prevalent in developing nations but there is not much of focus on these because perhaps one of the reasons is the economic reason. That is that, if you develop a new drug, the market is not able to purchase the drug for example, Ok.

So there is also something that has happened in the recent past. For example, malaria which has nearly been, it is almost non-existent in most of the developed nations is now seeing a resurgence in research in antimalarials. And this is because of tourism.

So lot of people from the west are traveling to fairly exotic countries where malaria is endemic. And so it also resulted in the spread of malaria in the southern states of the United States. So there is now focus on trying to figure out how to tackle this problem.

So these are some of the factors that are taken into consideration during deciding which disease to target.

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- Partnerships with governments and philanthropic organizations are now becoming common

So recently there has been resurgence in number of philanthropic organizations such as the Bill and Merinda Gates Foundation which is now partnering with governments, Ok. So governments of many countries are now taking an active interest in new drug discovery.

And this is because, since the pharmaceutical companies are focusing only on a subset of diseases, there are a number of other diseases which are important but not being worked on

by the industry which need to be addressed. And so these partnerships are now emerging to be very important in drug discovery.

So what these partnerships do is that they fund, you know sort of research that occurs even in basic research laboratories which are not necessarily in pharmacy but also in academic environments. And these are going to be the place from which new drug discovery can occur.

So choosing a disease is a fairly complex problem and a number of factors are going to be considered while doing this.

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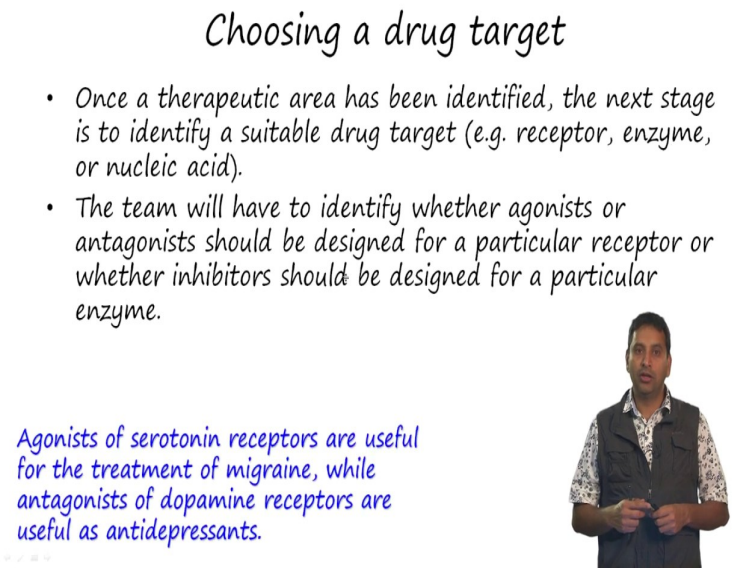

So once we have chosen a disease we need to choose a drug target, Ok. So once, so here we need to find a suitable drug target. We have already looked that in fair amount of detail about what are the major drug targets.

For example we have receptors or we have enzymes or of course

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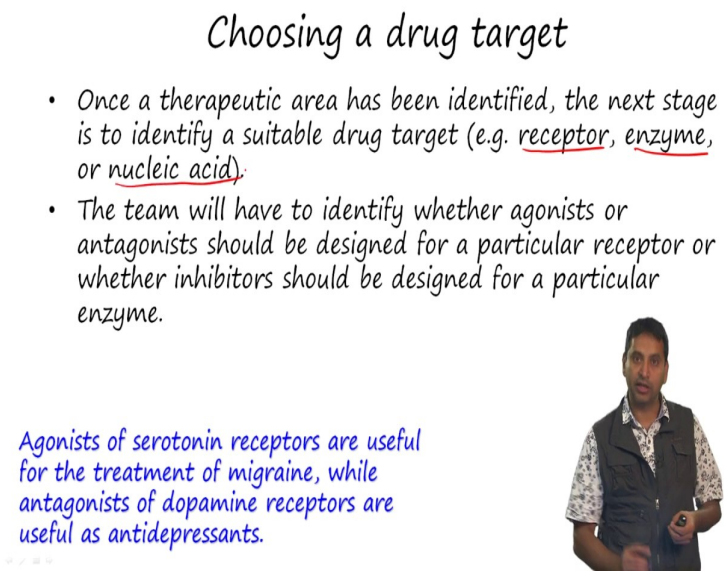

we have nucleic acids. And we have also looked at a variety of other drug targets that could be important as well.

And now so the research team will have to identify, for example if it is a receptor, whether one needs to develop an agonist or develop an antagonist, Ok. And if it is an enzyme whether it should be, what kind of an enzyme it is and whether inhibitor should be designed for a particular enzyme.

So for example agonist of serotonin receptors are useful for the treatment of migraine while the antagonists of dopamine receptors are useful

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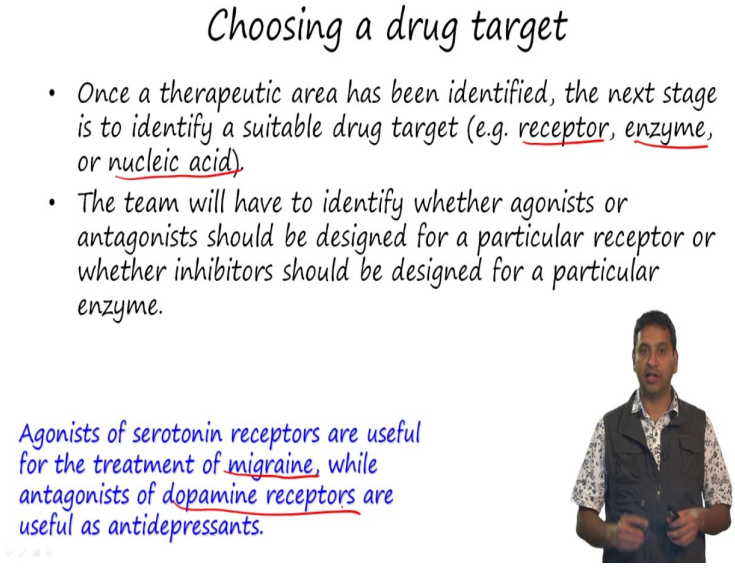

as anti-depressants.

So depending on what the drug target is one can figure out what kind of compound to be able to synthesize or develop.

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- Sometimes it is not known for certain whether a particular target will be suitable or not.
- For example, tricyclic antidepressants, such as **desipramine**, are known to inhibit the uptake of the neurotransmitter noradrenaline from nerve synapses by inhibiting the carrier protein for noradrenaline

Sometimes it is not known whether a particular target will be suitable or not.

So for example the anti-depressant compound desipramine whose structure is shown here,

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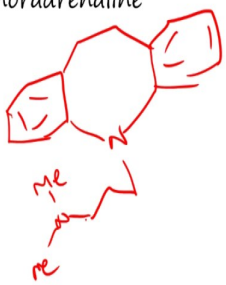
- Sometimes it is not known for certain whether a particular target will be suitable or not.
- For example, tricyclic antidepressants, such as **desipramine**, are known to inhibit the uptake of the neurotransmitter noradrenaline from nerve synapses by inhibiting the carrier protein for noradrenaline



as shown here, this are known to inhibit the uptake of neurotransmitter noradrenaline from nerve synapses by inhibiting the carrier protein for noradrenaline, Ok.

So

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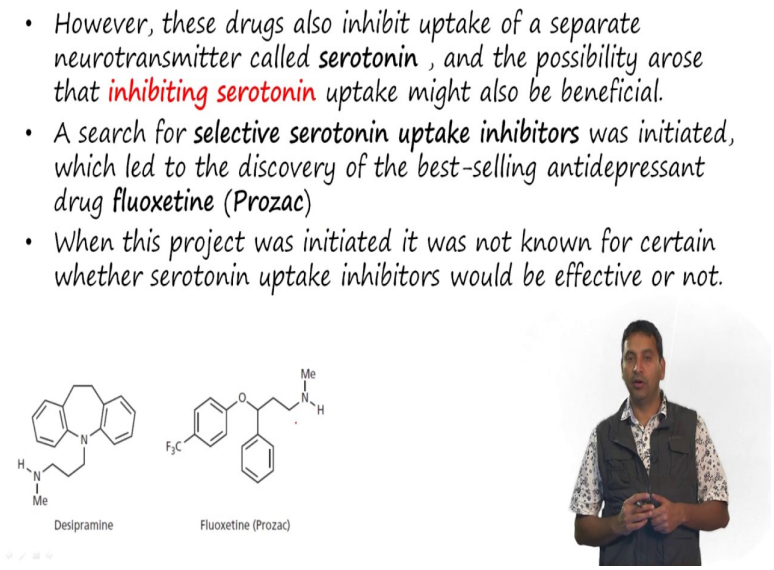

however these drugs also inhibit the uptake of a separate neurotransmitter known as serotonin. So the possibility arose of inhibiting serotonin because this has a very important implication in anti-depressants.

So what was figured out during the process was that inhibiting serotonin uptake would result in perhaps a new class of inhibitors and then a search for selective serotonin uptake inhibitor was initiated.

So essentially during the start of the project it was not known that serotonin uptake inhibition was useful and this resulted in the discovery of the, you know one of the best selling anti-depressant compound Prozac.

So therefore during the project process it is possible that we might make some interesting discoveries which can lead to very important drugs being developed.

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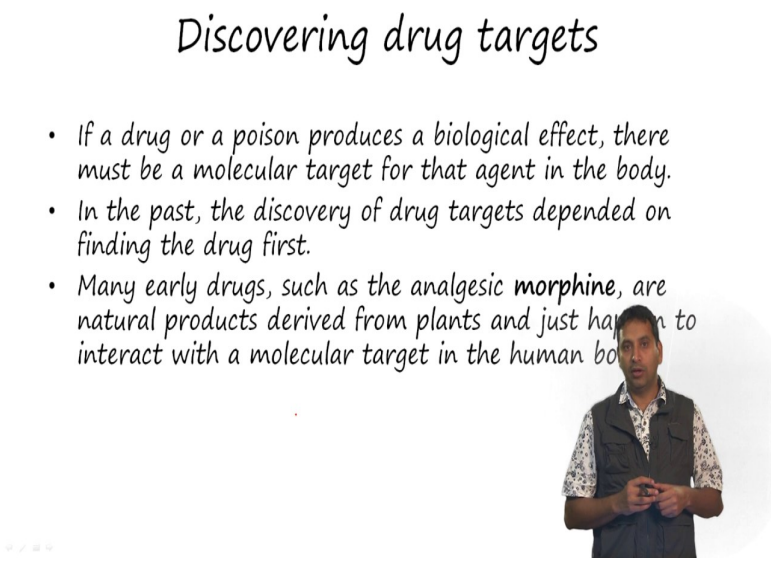

Now discovering drug targets is also something that one needs to be aware of. So if a drug or a poison produces a particular biological effect there must be a molecular target for that agent in the body. So that can be fairly reasonable to assume, right.

In the past the discovery of drug targets depended on finding the drug first, right. So for example you had morphine which was

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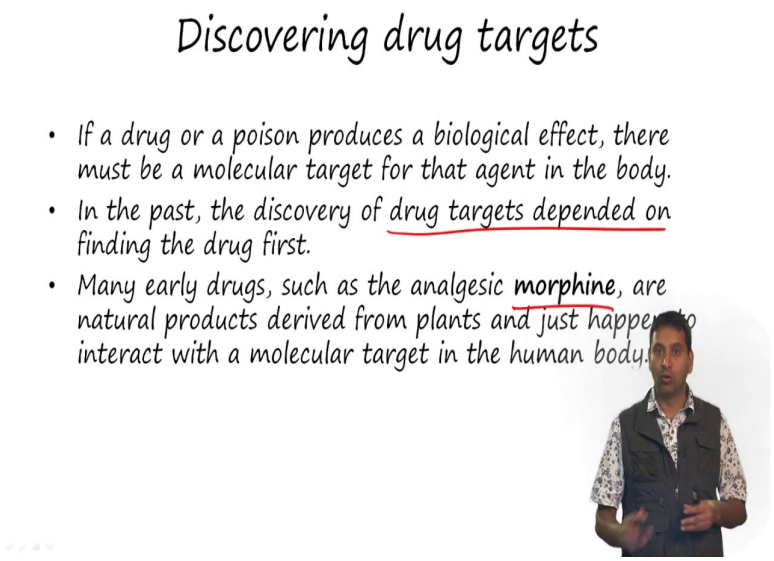

known to be an analgesic and it was used for many generations.

And it is known to be, you know it is obviously a natural product that is derived from plants but it just so happens to interact with the molecular targets in the human body.

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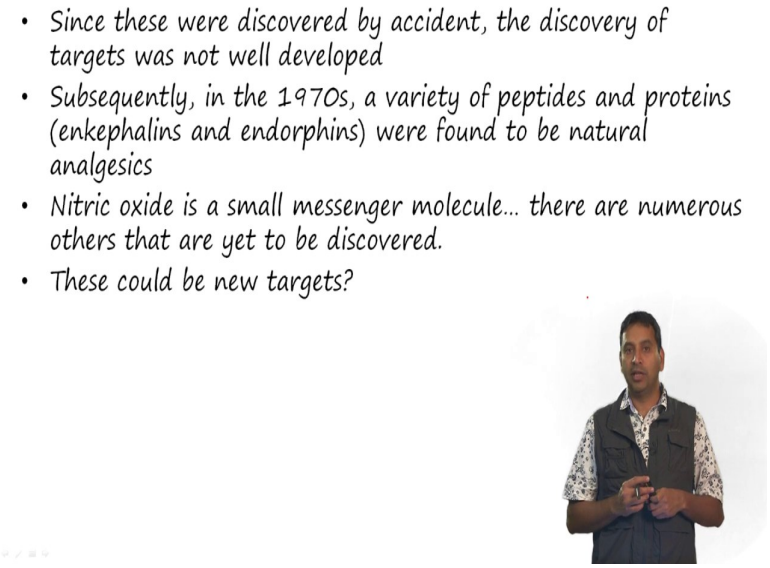

But then since these were discovered by accidents, the discovery of targets was not very well developed. In the 1970s a variety of peptides and proteins which were enkephalins and endorphins were found to be natural analgesics.

So this was an important discovery because at this point it was not known that these are actually going to be useful in analgesic activity.

So these discoveries will, will help us with identifying new drug targets as well. And separately in the 1970s and 80s, nitric oxide which is a small gaseous messenger molecule was also discovered and to be a important signaling agent, Ok.

So therefore inhibiting nitric oxide synthesis or enhancing nitric oxide generation can be new drug targets. Of course we should also keep in mind there are number of other targets that are yet unknown and yet to be discovered. And this is the active area of research currently.

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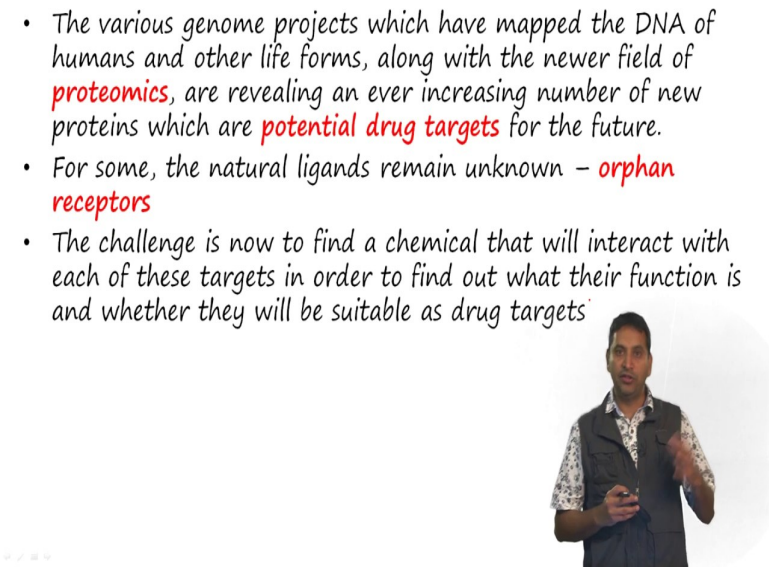

The genome projects which have been going on for several decades now have mapped the DNA of humans and other life forms.

And together with this new field of proteomics where one tries to figure out what happens inside the cell at the protein level, there is an increasing number of new proteins which are potential drug targets and once we identify these drug targets then we need to be able develop methodologies to target these or to inhibit these proteins, Ok.

There are also a number of natural ligands that are known but we do not know what the targets are, Ok. So these are termed as orphan receptors

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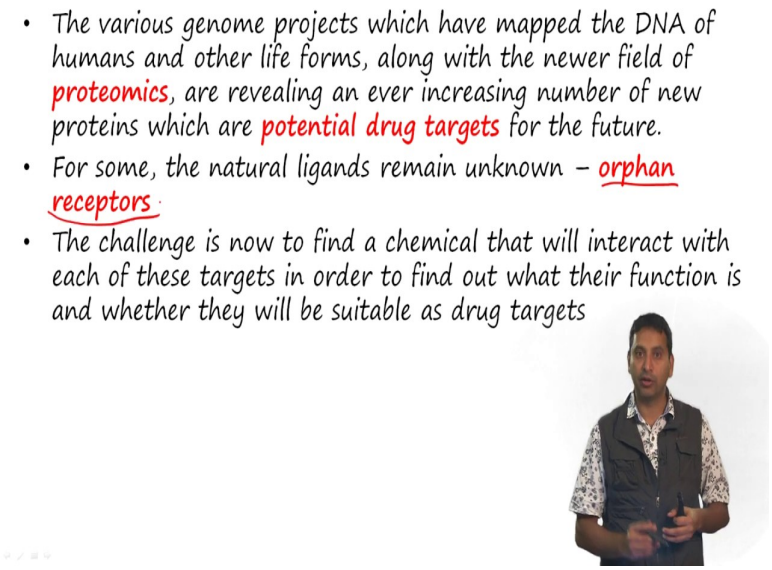

because we are unable to characterize where this ligand is actually hitting.

Now the challenge is now to find the chemical that will interact with each of these targets and in order to find out what their function is and whether they will be suitable as drug targets.

So these are some things that are important to consider when we are looking at drug targets.

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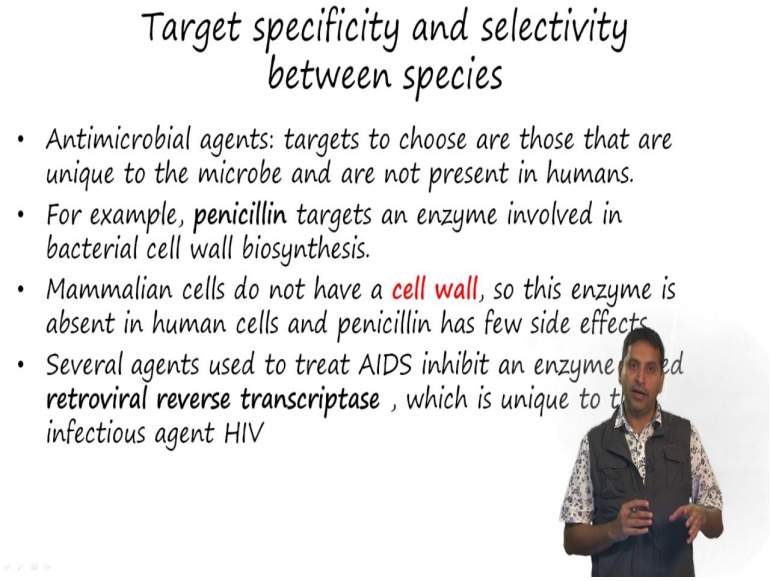

And once we have considered these, that is after we have chosen a disease and we have figured out what our drug target is, we also need to think about specificity and selectivity.

So antimicrobial agents which are basically antibacterials or antiviral compounds, they have to be, in order to develop these compounds the targets to choose are those that are unique to the microbe but are not present in humans.

If you recall, we started out this course by looking at the concept of magic bullet, this is exactly the same concept here. So we need to be able to selectively target proteins or DNA or anything that is present in microbe but not present in humans.

For example this antimicrobial penicillin targets an enzyme involved in the cell wall biosynthesis. We look at this in detail in later part of the course. And since mammals do not have a cell wall. Ok, so this enzyme is absent in humans.

Penicillin has very few side effects, Ok. There are also other examples such as, you know the reverse transcriptase enzyme which is present in the human immunodeficiency virus HIV which causes AIDS but it is not present in humans. And therefore this becomes unique enzyme to the

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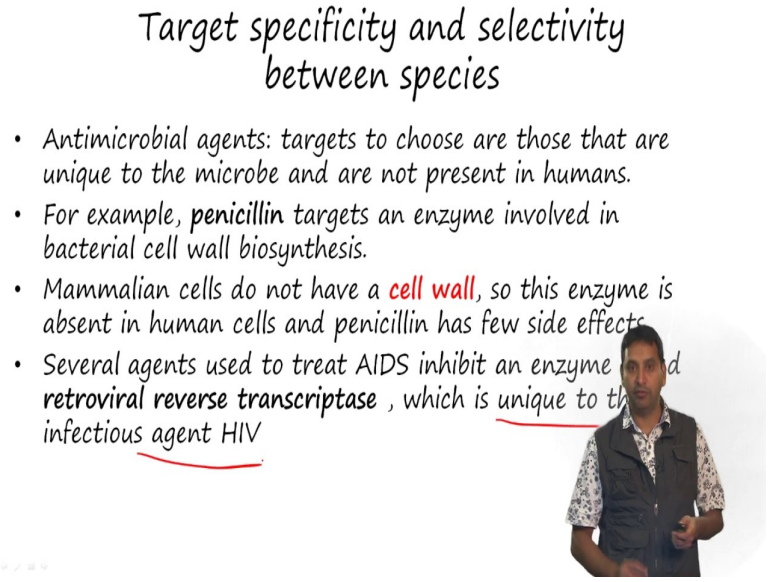

infectious agent HIV.

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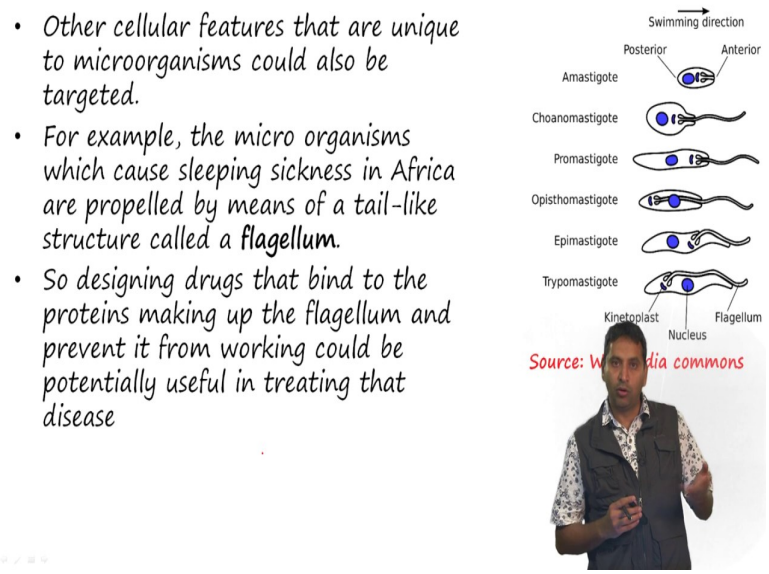

There are also other cellular features that are unique to microorganisms that can also be targeted. So for example there is this disease called as sleeping sickness in Africa which is caused by trypanosomes. And these microorganisms are propelled by means of tail-like

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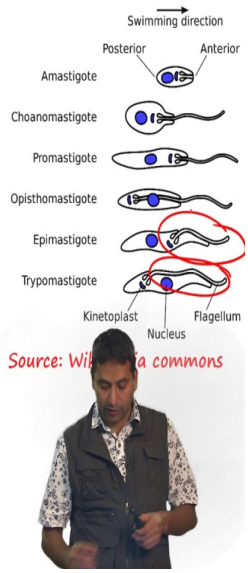
- Other cellular features that are unique to microorganisms could also be targeted.
- For example, the micro organisms which cause sleeping sickness in Africa are propelled by means of a tail-like structure called a **flagellum**.
- So designing drugs that bind to the proteins making up the flagellum and prevent it from working could be potentially useful in treating that disease



structure called as the flagellum.

So since this is a very unique structural feature in this microorganism we could design drugs that could bind to the proteins made up of the flagellum and prevent it from working.

So once you prevent it from working then this

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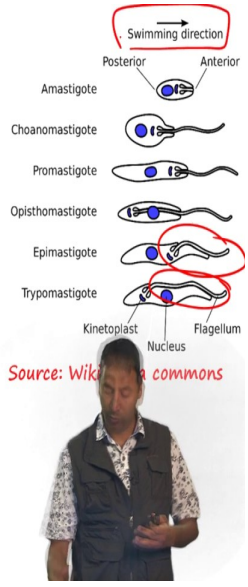

entire propelling motion is going to be inhibited and its infectious nature is going to get put out.

So this could be a target that one could think about.

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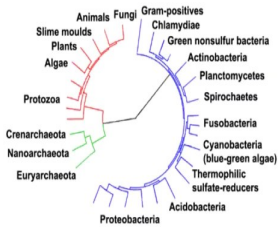
- It is not always necessary for the enzyme to be absent. Even differences among similar enzymes in both species can be exploited...
- The enzymes may have been derived from an ancient common ancestor, but several million years of evolution have resulted in significant structural differences.



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Of course it is always, it is not necessary that the enzyme or the target be absent. So even in differences among similar enzymes can be exploited.

So here is the common ancestry evolutionary tree and as you can see in this evolutionary tree, a similar, an enzyme which could have evolved, you know many centuries back or from a common ancestor can evolve in such a way that there are significant structural differences.

So the difference between gram positive enzyme

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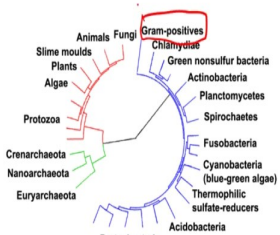

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and the same enzyme in animals

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- It is not always necessary for the enzyme to be absent. Even differences among similar enzymes in both species can be exploited...
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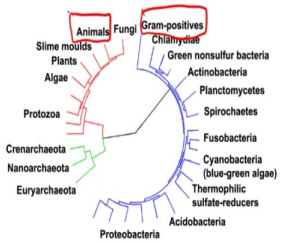

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or the protein in animals could be quite significant. And so there are multiple aspects to this. So there could be an enzyme which has fairly quite different structure.

And this structure could manifest itself in the function also. But these differences in the structure may not manifest in the function which means that it can still play the same function but it has a different structure.

So therefore in this particular case we can exploit these differences, structural differences to develop new drugs. So this is something that, that is very useful in identifying drug targets.

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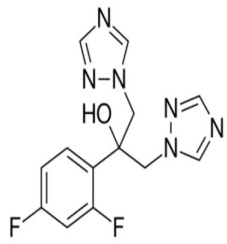
- For example, the antifungal agent **fluconazole** inhibits a fungal demethylase enzyme involved in steroid biosynthesis.
- This enzyme is also present in humans, but the structural differences between the two enzymes are significant enough that the antifungal agent is highly selective for the fungal enzyme.



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So an example here is the antifungal agent fluconazole. It inhibits an enzyme known as fungal demethylase

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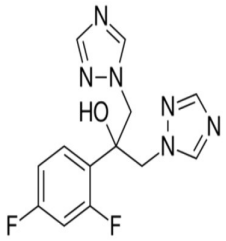

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which is involved in steroid biosynthesis.

The human counterpart for this enzyme is also present but structural differences are quite significant that the antifungal agent is highly selective for the fungal enzyme.

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- Other examples of bacterial or viral enzymes which are sufficiently different from their human equivalents are dihydrofolate reductase and viral DNA polymerase

So there are number of other examples of bacterial or viral enzymes which are sufficiently different from the human equivalents and some examples are dihydrofolate reductase and viral DNA polymerase.

We will again look at some of these examples later on in the course but suffice to say at this point that it is not necessary that the enzyme is completely absent. Even if the enzyme is fairly different in bacteria versus human, one could use this as a target.

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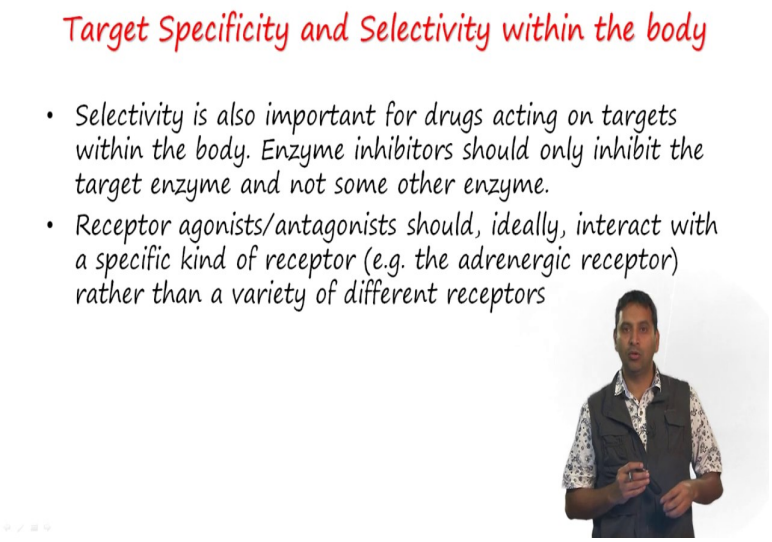

Now after you have figured out the specificity of the target we also need to figure out the specificity of the target within the body, that is if the particular enzyme or receptor is present in all cells and in an identical manner then once we administer the drug it is going to hit all parts of the body which is not desirable.

So within the body, among various cell types inside our body we need to be able to have some selectivity. And this is very important because we do not want side effects to occur during drug administration.

So enzyme inhibitor should only inhibit the target enzyme and not some other enzyme. Now there are receptor agonists or antagonists which we are proposing to discover or develop should ideally interact with a specific kind of receptor, for example the adrenergic receptor but rather than a variety of different receptors.

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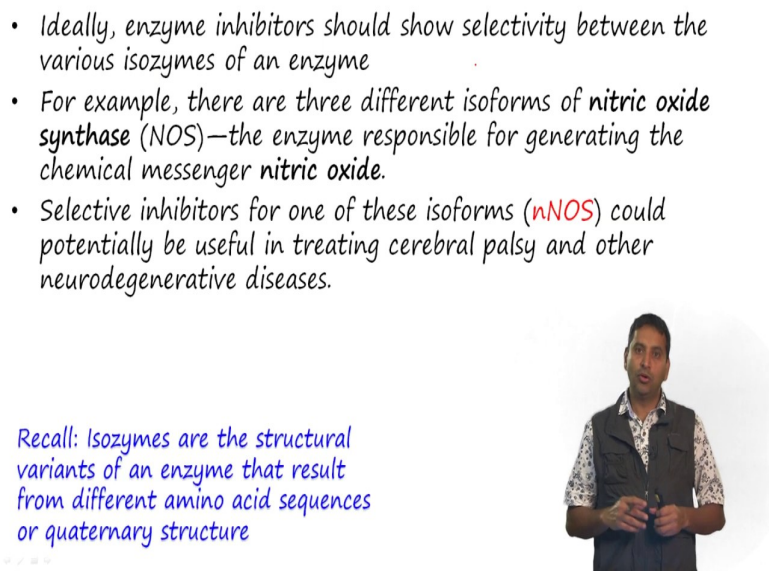

So ideally an enzyme inhibitor should also show selectivity between various isozymes of an enzyme.

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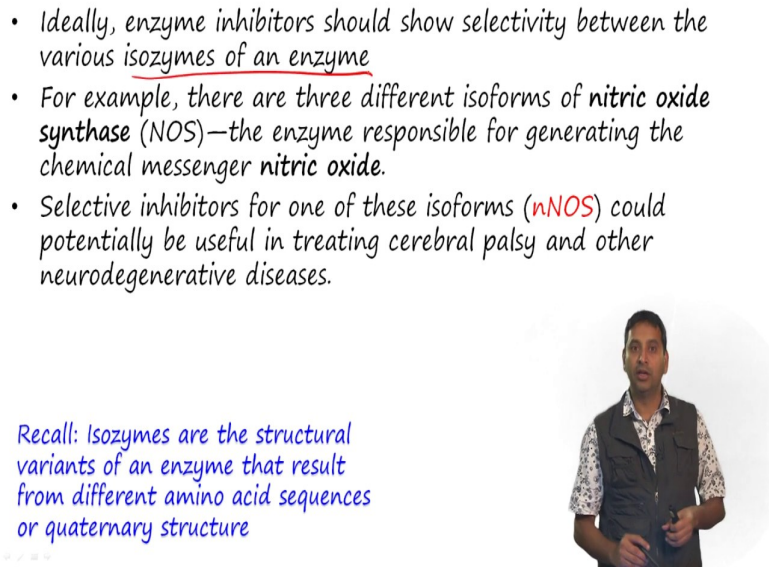

You may recall that the isozymes are the structural variants of an enzyme that result from different amino acid sequences or quaternary structure.

So for example there are 3 isoforms of nitric oxide synthase which is the enzyme responsible for generating nitric oxide. Now selective inhibitors of one of these isoforms which is the neuronal nitric acid synthase or nNOS

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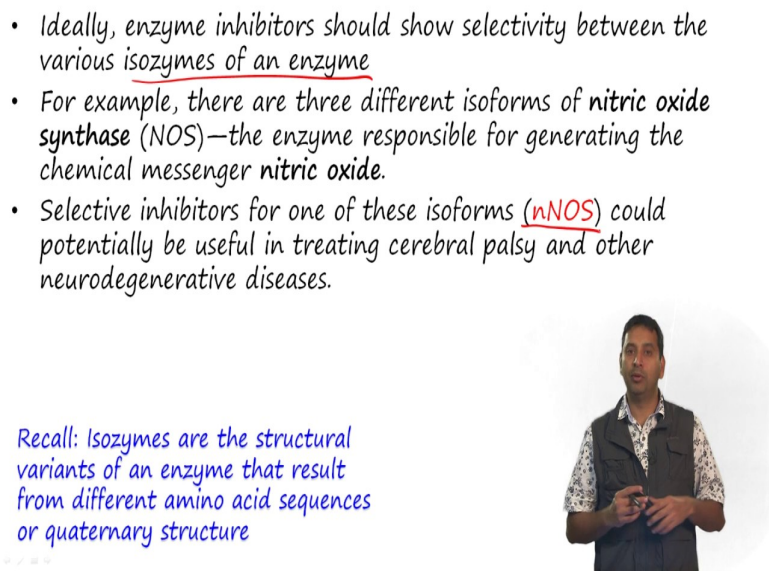

could be potentially useful in treating cerebral palsy and other neuro degenerative disorders.

But it is an immense challenge to be able to figure out a inhibitor that selectively inhibits only this isoform. Because if you inhibit the other isoforms, it can also be potentially harmful to the body.

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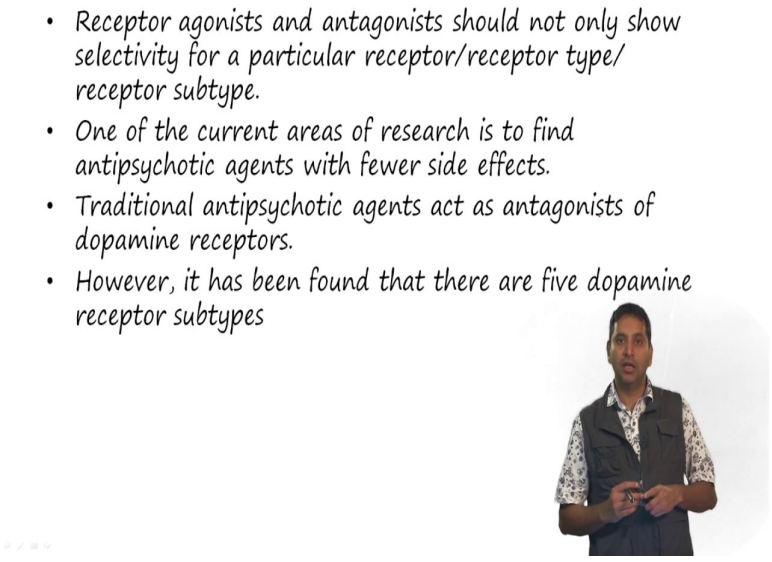

Similar receptor agonist and antagonist should not only show selectivity for a particular receptor, receptor type but also receptor subtype. One of the major areas of research is to find anti-psychotic drugs with fewer side effects, Ok.

This is because traditional anti-psychotic agents act as antagonists of dopamine receptors. However it has been found that there are 5 dopamine receptor subtypes.

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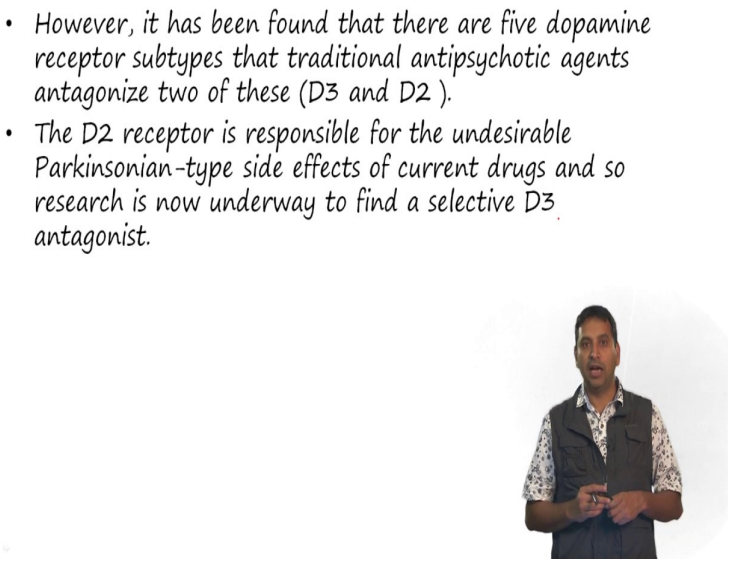

And because of this, the traditional anti-psychotic agents antagonize two of these which is D3 and D2. But the D2 receptor is responsible for the undesirable Parkinsonian type side effects of these currently used drugs. And so we need to be able to find a way to only hit D3 rather than D2.

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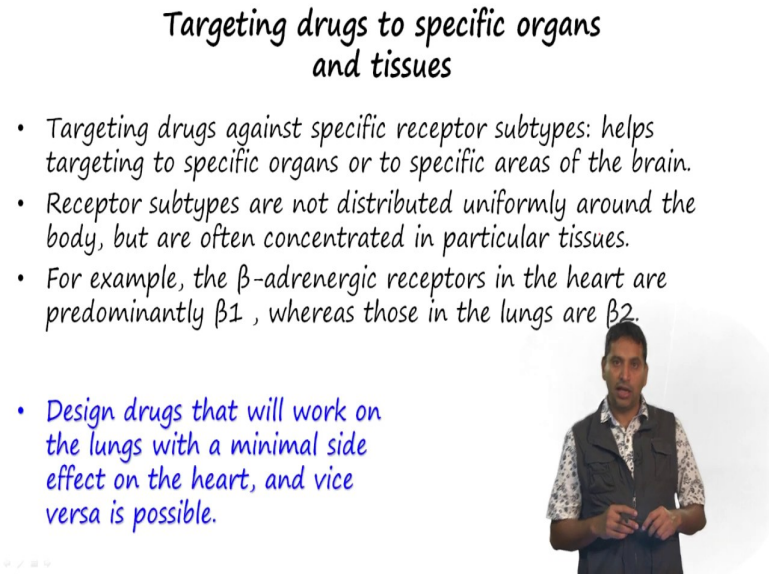

Lastly we also need to be able to target drugs to specific organs and tissues. So this basically means that, let us say we want to develop a drug for specific area of the brain, we should be able to spare the rest of the body.

Or if we want a drug to be, sort of acting on the, on the liver we do not really want it to be being metabolized in other places, or being active in other places. So what we need to do here is that receptor subtypes are not uniformly distributed, Ok. And they are often concentrated in particular tissues.

So for example the beta adrenergic receptors

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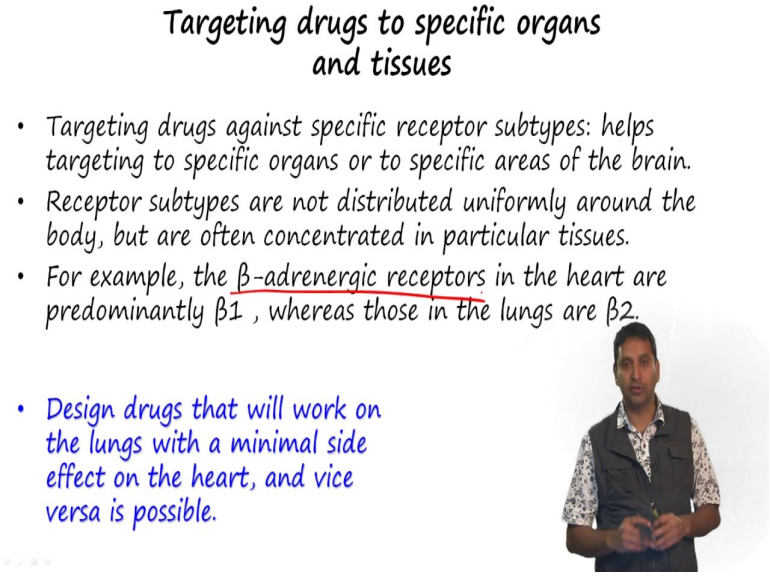

in the heart are predominantly beta 1 whereas those in the lungs are beta 2.

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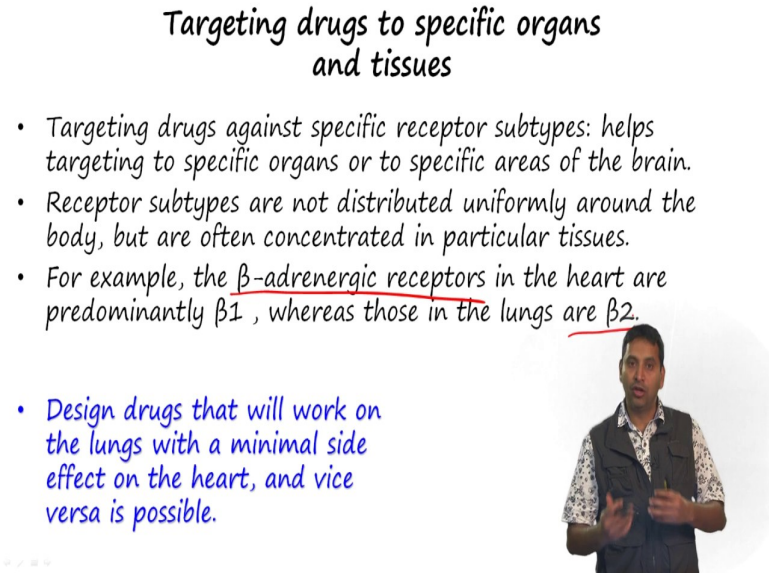

So if you are able to design a compound that is able to modulate beta 1 then it is going to be activated predominantly in the heart and while it will spare the lung.

So we need to be able to design drugs that will work on the lungs, for example with the minimal side effect on the heart and vice versa. And both of these are possible if you are able to achieve selectivity.

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- Attaining subtype-selectivity is particularly important for drugs that are intended to mimic neurotransmitters.
- Neurotransmitters are released close to their target receptors and, once they have passed on their message, they are quickly deactivated and do not have the opportunity to 'switch on' more distant receptors

But attaining selectivity is very challenging. But it is also important for drugs that mimic neurotransmitters.

Neurotransmitters as we have discussed previously are released very close to their target receptors. And once they have passed on their message, they are quickly deactivated. So they are either taken up by the cell or they are destroyed, right.

And so they do not have the opportunity to switch on more distant receptors. So once the signaling is done it is not going to go to and interact with the cell which is further away.

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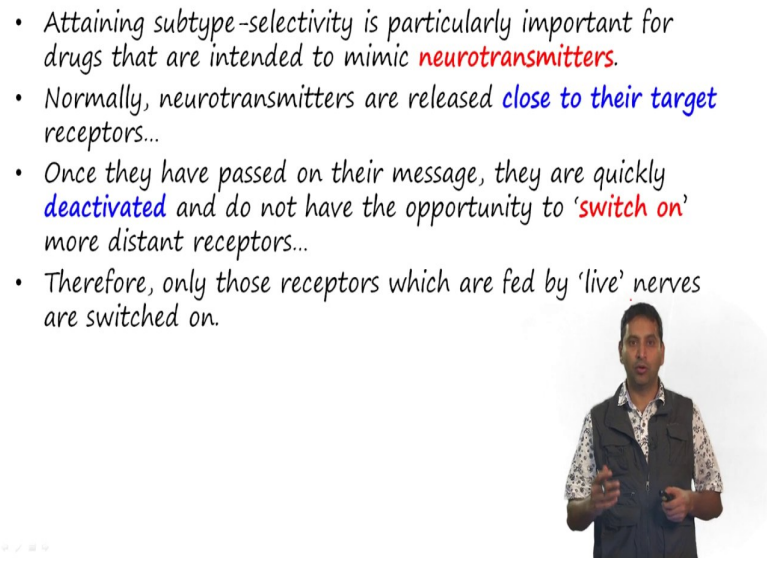

So therefore only those receptors which are fed by live nerves are switched off.

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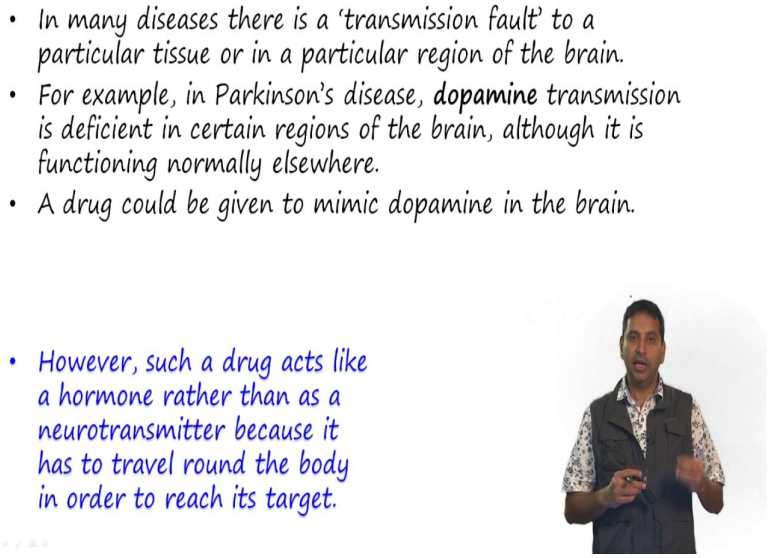

In many diseases there is a transmission fault, Ok which means that there is a particular region of the brain which does not receive the signal, Ok. So for example in Parkinson's disease, dopamine transmission is deficient in certain regions of the brain although it is functioning normally elsewhere.

So if we can develop the drug that can mimic dopamine in the brain then that would be very useful. However once we give a drug or administer the drug such as this, what happens is that the drug acts as a hormone rather than as a neurotransmitter.

We have already spent some time on distinguishing a neurotransmitter from a hormone. But one of the major features is that the hormone is secreted by glands and then it has to travel a substantial distance for it to reach the cell of interest or receptor of interest.

So here we want the drug to act like a neurotransmitter but it actually acts like a hormone. So since it travels around the body to reach its target, it has a number of side effects that are undesirable.

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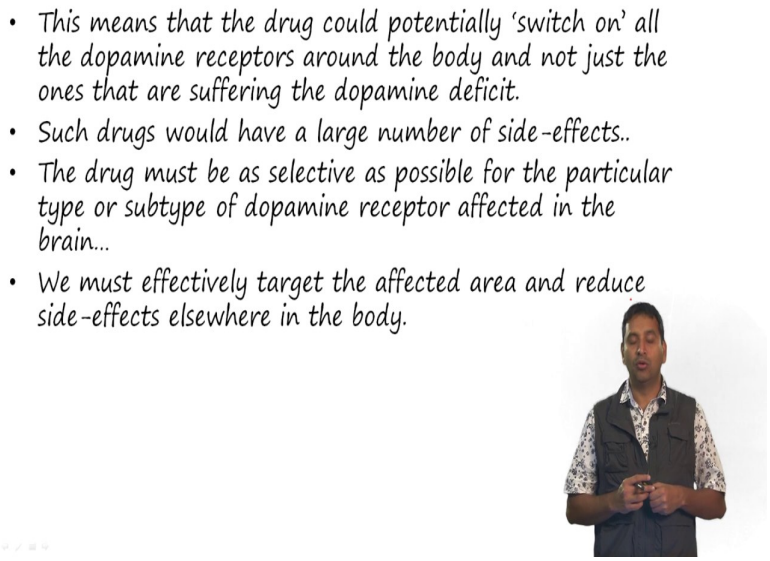

So what this means is that the drug could potentially switch on all the dopamine receptors around the body and not ones that are just suffering from the dopamine deficit.

So there are, as you can imagine there are number of side effects. So the drug that we intend to develop must be as selective as possible for the particular type or subtype.

Then we would be able to effectively target the affected area and reduce the side effects elsewhere in the body.

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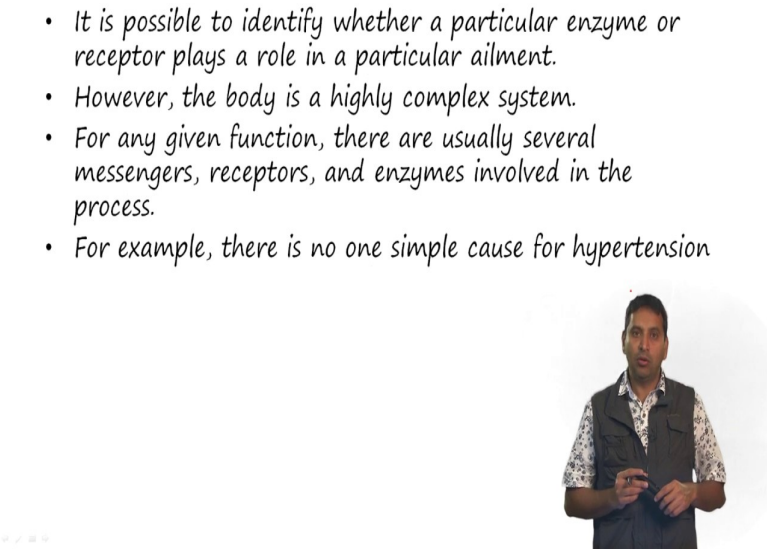

Now it is possible to identify whether a particular enzyme or receptor plays a role in a particular ailment,

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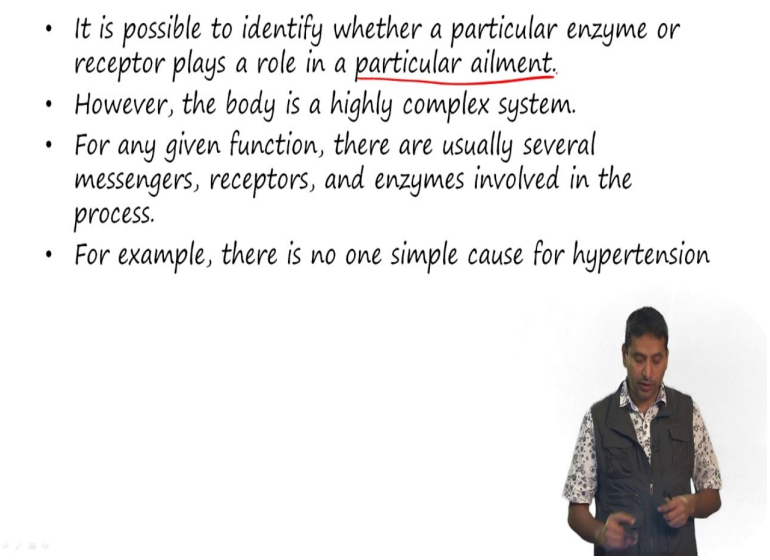

Ok.

However the body is an extremely complex system. So for example if the, you know if you are looking at this disease of hypertension which is high blood pressure there are number of messengers, receptors and enzymes that are involved in this process.

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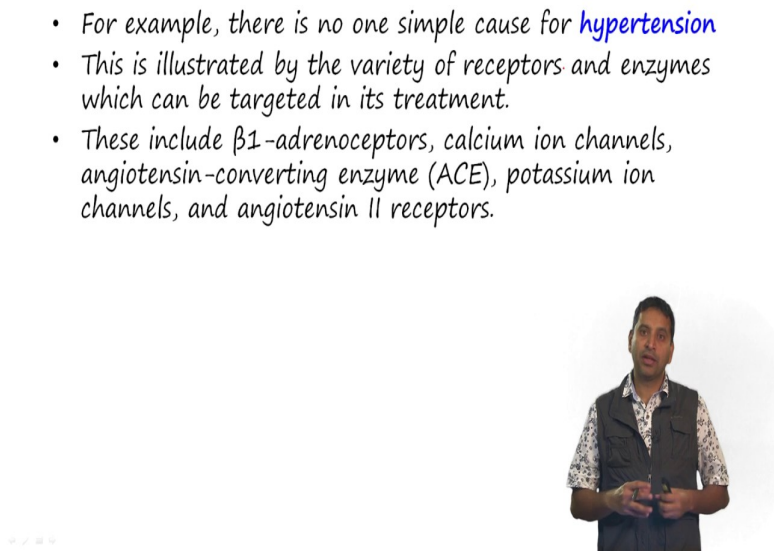

So hypertension for example involves the beta 1 aderenoceptor, calcium ion channel, angio-tensin converting enzyme which is ACE, potassium ion channels, angio-tensin 2 receptors and so on and so forth.

So to treat this complex ailment of high blood pressure

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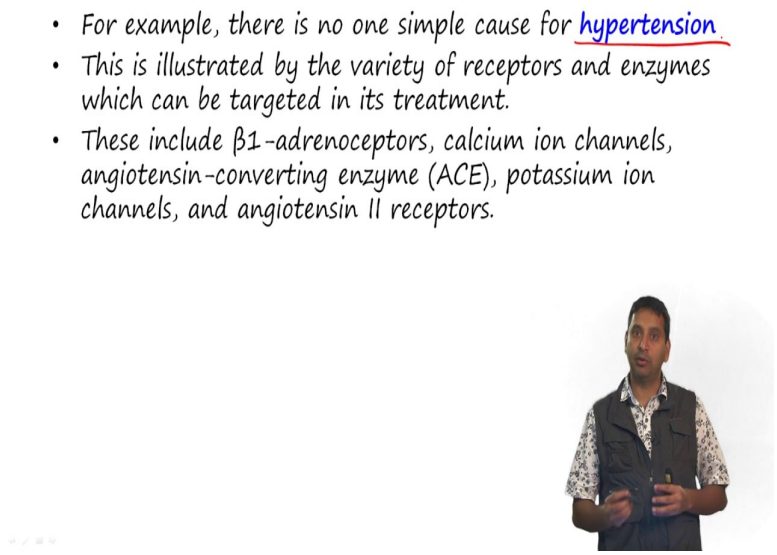

or hypertension one needs to consider this entire complex system, Ok.

So looking at a phenotype that means looking at reduction of blood pressure as the goal would be useful but achieving selectivity is also going to be something that we would look forward to, because you could have drugs which are hitting particular targets

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- For example, there is no one simple cause for hypertension
- This is illustrated by the variety of receptors and enzymes which can be targeted in its treatment.
- These include β1-adrenoceptors, calcium ion channels, angiotensin-converting enzyme (ACE), potassium ion channels, and angiotensin II receptors.

rather than all of them.

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- Sometimes, drugs designed against a specific target become less eff ective over time.
- Because cells have a highly complex system of signalling mechanisms, it is possible that the blockade of one part of that system could be bypassed.

Sometimes drugs designed against a specific target become less effective over time. And this is because cells have a highly complex system of signaling and it is possible to block one part of it but the system can be bypassed.

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- This could be compared to blocking the main road into town to try and prevent congestion in the town centre.
- To begin with, the policy works, but, in a day or two, commuters discover alternative routes, and congestion in the centre becomes as bad as ever

So the analogy that we are looking at is for example, if there is a town center let us say that, this is the center of the town and we want to reduce the traffic

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- This could be compared to blocking the main road into town to try and prevent congestion in the town centre.
- To begin with, the policy works, but, in a day or two, commuters discover alternative routes, and congestion in the centre becomes as bad as ever

in this area, Ok.

So what we would do is that there are 3 major roads which are connecting this area,

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- This could be compared to blocking the main road into town to try and prevent congestion in the town centre.
- To begin with, the policy works, but, in a day or two, commuters discover alternative routes, and congestion in the centre becomes as bad as ever

Ok. So

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- This could be compared to blocking the main road into town to try and prevent congestion in the town centre.
- To begin with, the policy works, but, in a day or two, commuters discover alternative routes, and congestion in the centre becomes as bad as ever

you can enter the town center from here or you can enter it from here or enter it from here,

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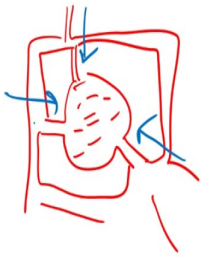
- This could be compared to blocking the main road into town to try and prevent congestion in the town centre.
- To begin with, the policy works, but, in a day or two, commuters discover alternative routes, and congestion in the centre becomes as bad as ever



Ok. So if you want to reduce vehicular traffic in this area, what you would do is to put a barrier over here,

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- This could be compared to blocking the main road into town to try and prevent congestion in the town centre.
- To begin with, the policy works, but, in a day or two, commuters discover alternative routes, and congestion in the centre becomes as bad as ever

for example, right.

Now what this does, this clearly reduces the flow of traffic from this direction and you may have less amount of cars in that area.

But what can also happen is that after some time the trucks start to

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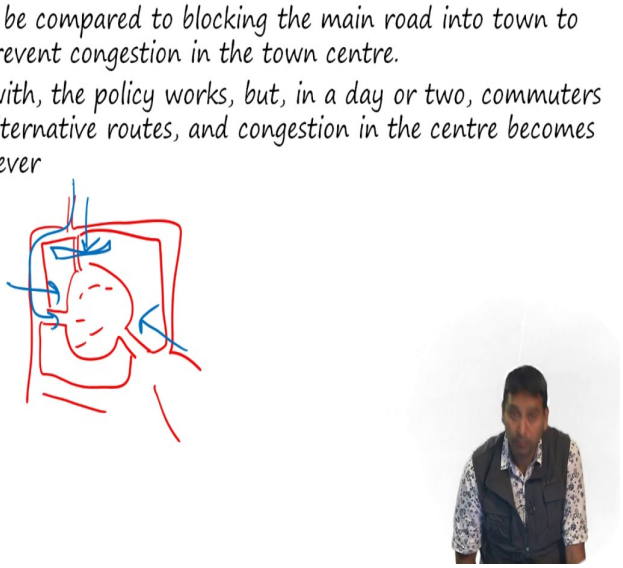

come or the vehicles start to come from this direction. Or start to come

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from this direction.

And then they start to repopulate this, Ok. So this is a good analogy to understand how one can develop a barrier but there could be other mechanisms or other ways in which the same phenotype can be expressed.

So what happens is that this is something that we need to watch out for when we are discovering new drugs.