Medicinal Chemistry
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Prodrugs
Mod09_Lec51

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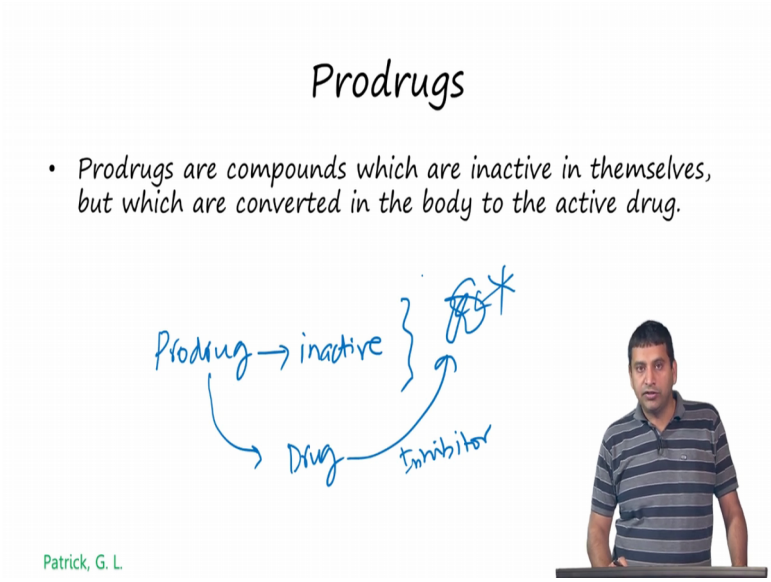

Welcome back in today's lecture we are going to deal with prodrugs, so prodrugs we have looked at them in briefly previously and basically they are compounds which are derivatives the active drug and they themselves are actually inactive, so that means that if I just administered them we are going to be inactive but inside the body. Once they get into the body than there metabolized or they are converted by some enzymatic reaction pretty much to form the active drug.

So what this means is that is like almost like a sleeping drug, so myself it is not active, but it is converted to an active form, so if you see this concept, so prodrugs would be inactive means let say I screen for an inhibitor of an enzyme okay, and this product is itself is does not have any activity. Okay, but what happens is that it gets converted to the active drug which can then inhibit the enzyme okay, so the concept is that the reason you want to use this is because many times the drug itself might a little bit toxic or may have many side effects and so if you want to reduce the side effects when you want to send the drug specifically to the area of interest where this enzyme is present. Okay, so the concept is very straightforward and there are many successful examples of prodrugs.

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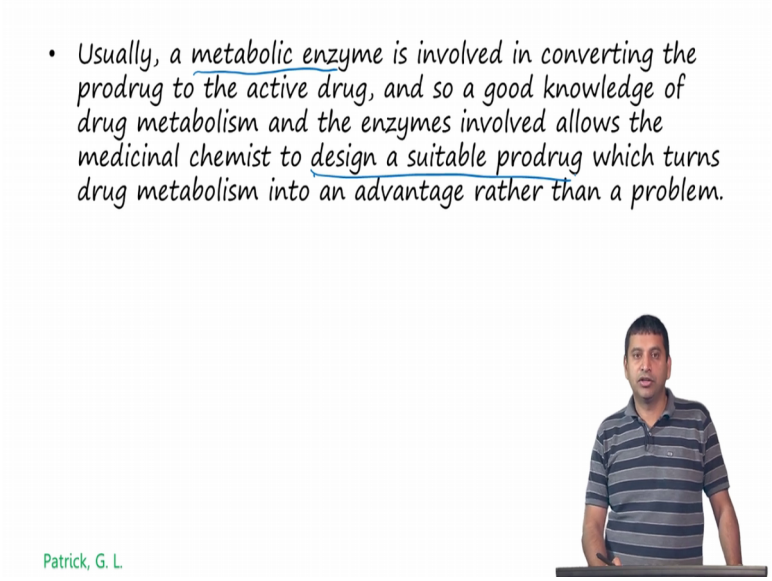

So I implicit in this concept is the requirement of a metabolic enzyme, so this metabolic enzyme what it does is basically it converts the prodrugs to the active drug, so for us to design good prodrugs we would need a very good knowledge of drug metabolism and we also need to know in detail the enzymes that are involved in this process, so once we have a good knowledge of this, so we have already studied extensively about ADME which is basically absorption, distribution, metabolism and excretion, so here the M which is the metabolism, we have already studied in detail and so once we know what are the enzymes that are involved and what are the type of reactions that are informed, then we would be able to design a suitable product, which then is design to go into the body get metabolized and form a active drug, okay, so here what you are doing is we are taking advantage of drug metabolism rather than addressing it as a or thinking about it as a problem.

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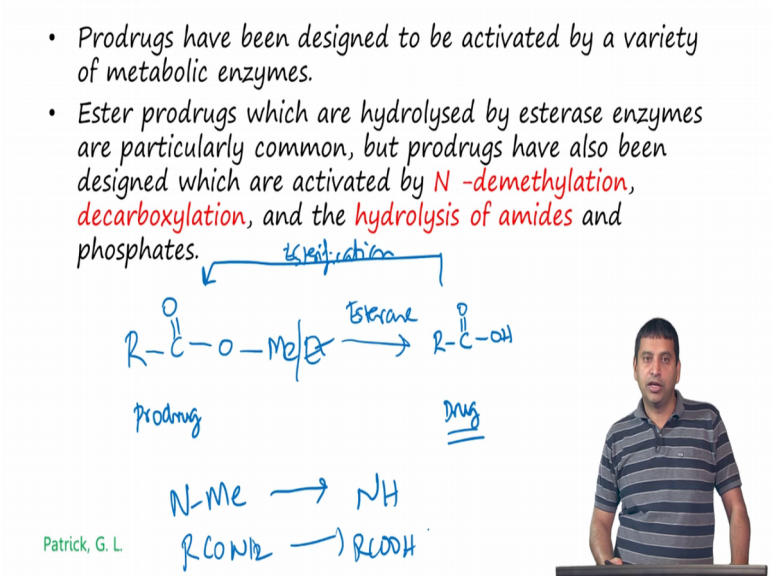

So prodrugs have been designed by a variety of metabolic enzymes, so there are perhaps about twenty, thirty examples of various metabolic enzymes, we will look at only a few of them, so this metabolic enzymes there should be, you know enzymes which are able to turn over your prodrugs into the active drug, the most common example is esters, so here you have R which is your drug, let say drug has a free carboxylic acid, then one could make a methyl ester or an ethyl ester of this molecule.

Now, in the presence of esterase okay, what you would expect would happen it will form R C double bond O, OH, okay, so here is the prodrugs and here is the drug okay, now in terms of synthesis what would you do is you would just do an esterification right, to convert the carboxylic acid to the ester, so this is a very straightforward examples, but you can also have other examples such as N demethylation, where you have a N methyl group which you have already looked at can be de-methylated to form NH, you can also have decarboxylation as in the case of L-dopa and hydrolysis of amides.

So when you have amides can have, you know hydrolysis which is basically R CONH2 which will form R COOH right and so on and so for, so all of these can be used and of course phosphates can also be hydrolyse to give you the corresponding hydrolysed atom.

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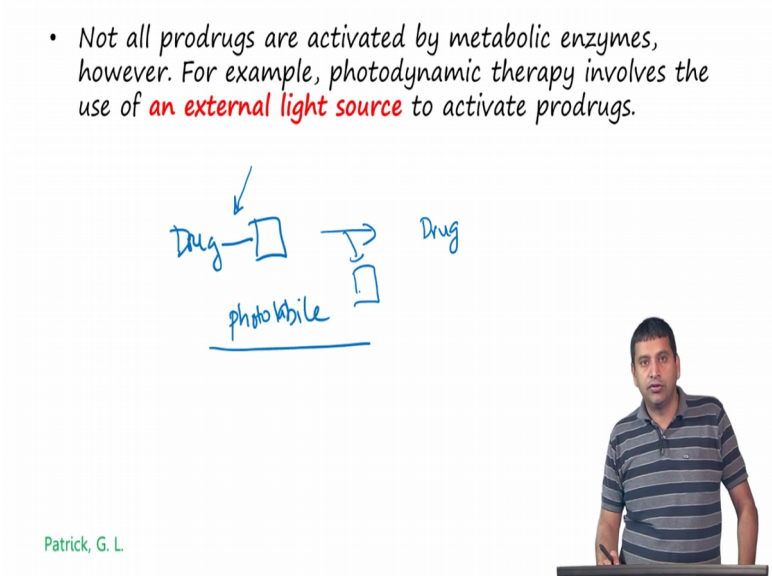

So there is a minor point here which will look at in more detail later, which is that not all prodrugs are activated by metabolic enzymes, so the definition of prodrugs is that they typically used by metabolic enzymes but there are examples of using an external light source, so what these do? Is it, this is call as photodynamic therapy, so here we have a drug which is attached to molecule and this molecule is actually what is known as photo labile okay, what this means is that?

The molecule is going to get cleaved under light, so here is your light source and if it is going to get cleaved, then informs the drug and it will give out this attachment okay, so this is again been used white extensively, especially in cancer therapy where you can localise the drug by using an external light source, will look at this or in detail in the later part of this lecture okay.

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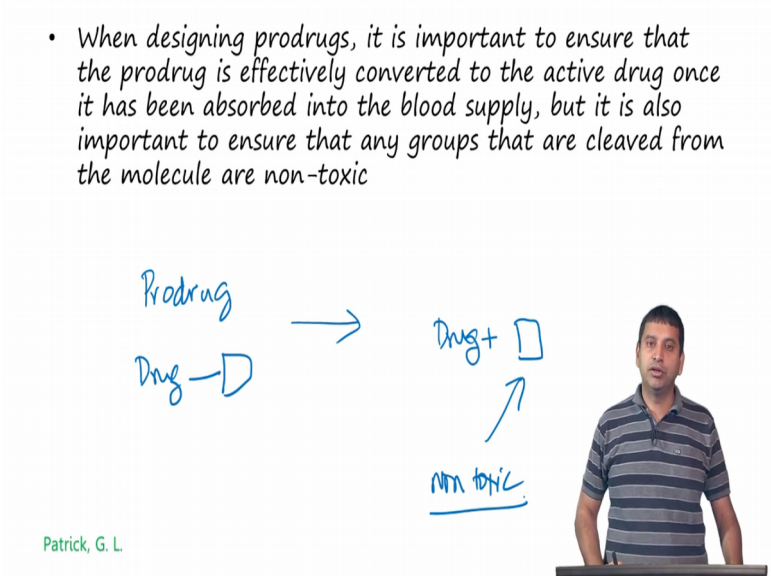

So what we need to keep in mind when we are designing this prodrugs is that we need to ensure that the prodrugs is effectively converted to the active drug once it is absorbed into the blood supply, of course, you have to ensure that any groups that are cleaved are non-toxic, so what this means is that, let say you have a prodrugs in the form of drug and it has an appendage, now when it forms the actual drug it is going to give away this appendage and this should be non-toxic okay. so, whatever that falls out, if it turns out to be toxic then it becomes a huge problem because then we are dealing with toxicity issues associated with the by-product.

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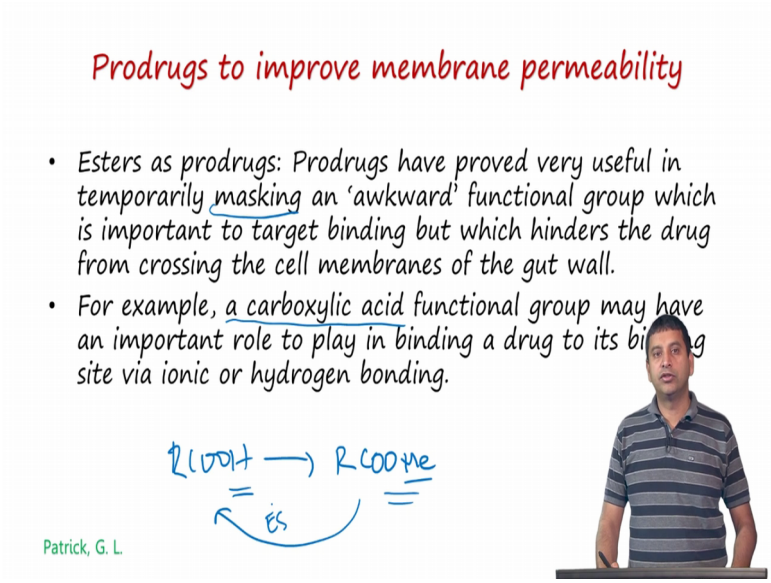

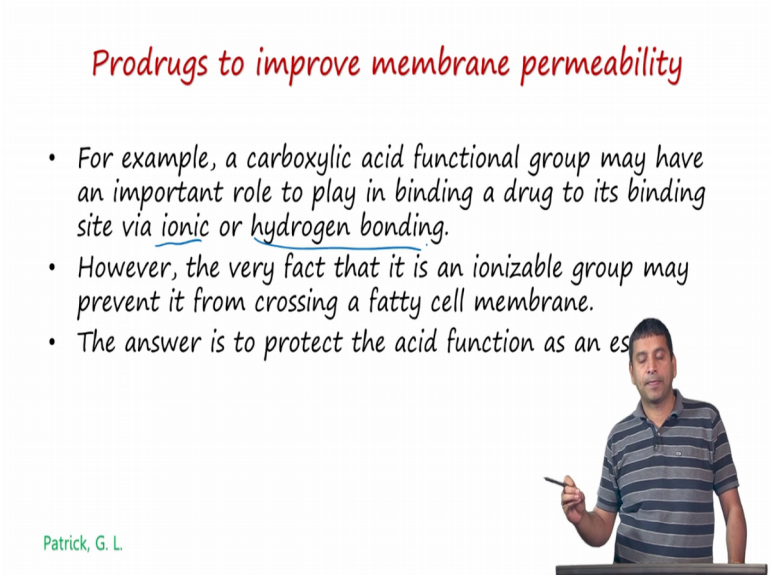

Okay, so now what will do is? Will study or will look at in detail a some of the various approaches to do to prodrugs, so the first approach is to work on improving membrane permeability okay, so we have already looked at you know, many examples of how the various functional groups in a molecule that are going to help with membrane permeability, but there are certainly functional groups which you do not help with this, so basically you have for example, a carboxylic acid which does not help you with permeability because the leopard membrane is quite hydrophobic and the carboxylic acid, which will probably exist as carboxylate will not permit the barrier.

So this results in a situation where you have a very nice drug what is not able to get across the cell membrane, so in order to masked this what people do is we converted into a an ester, so this provides a temporary mask, so you can what a carboxylic acid R COOH to the corresponding ester in this case, we can think about a methyl ester or an ethyl ester and what it does is that because you have converted a highly polar group to a less polar group, the membrane permeability improves okay.

Once it gets into the cell than what happens is that ester S is going to cleave it and give you back the active carboxylic acid, so this is one way in which we can temporary masked an awkward a group which is obviously important for target binding, but it is not able to read into the cell.

So this as we discussed this carboxylic acid, there are many drugs which carboxylic acids and they are very good with ionic or hydrogen bonding interactions and so when we prevent this interaction from happening the ester itself would not be very active and therefore it become

useful. Okay, so the very fact that an ionizable group may prevented from crossing fatty cell membrane, is something that has led to a number of esters, so we can now make a number of esters which have various permeabilities and various stabilities okay.

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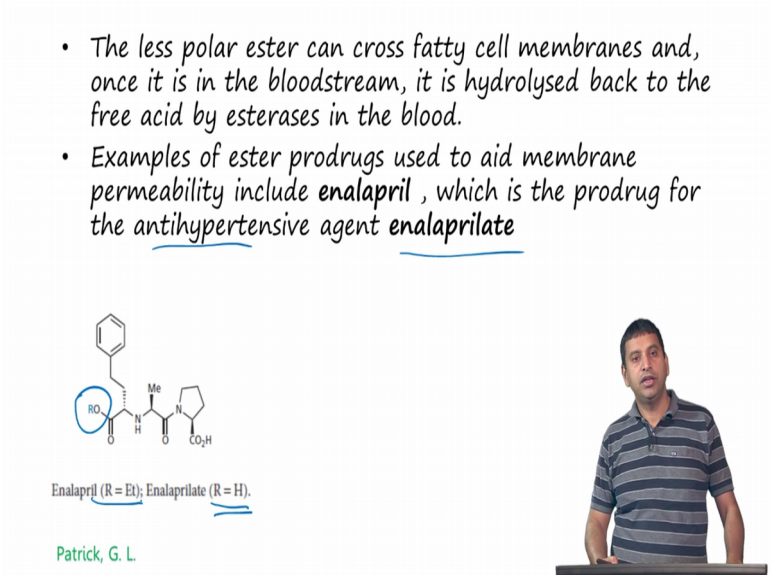

Now, for example, can look here is the this molecule called as enalapril, which is actually a prodrugs of the antihypertensive agent enalaprilate okay, so here is the molecule where R equals H is the active drug and this is the ethyl ester which will produce ethanol as a by-product and these are cleaved by esterases the bloodstream, so what it helps with is that it helps with getting the molecule cross the membrane and once it gets into the bloodstream, it can, then can cleaved by esterases to produce the active compound.

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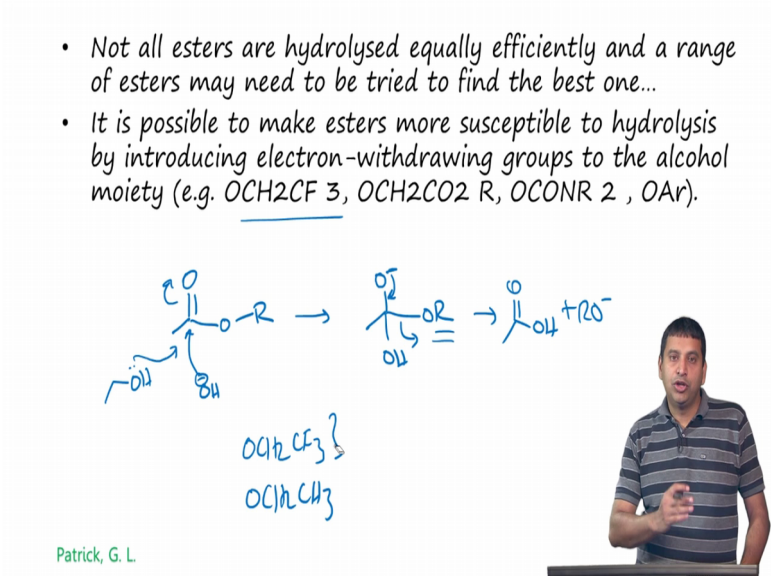

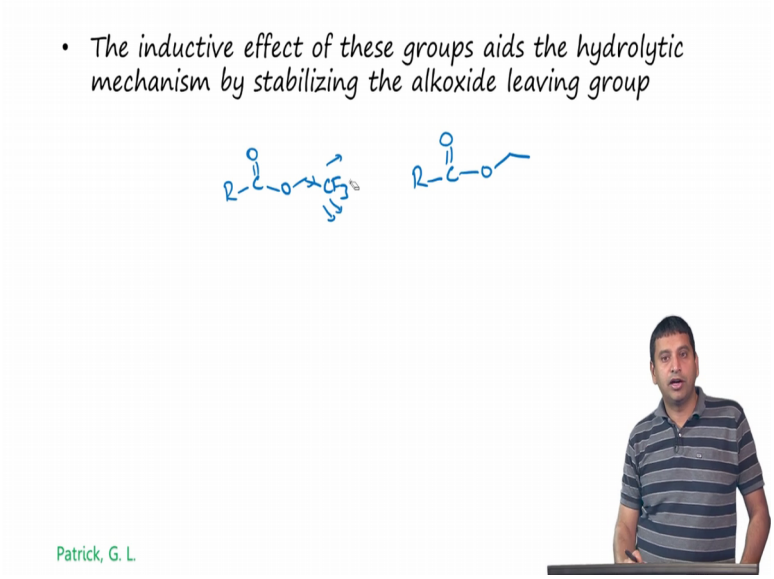

Now not all esters are equally efficient in getting hydrolysed, so which we can very well imagine would be a function of the living group ability, so if you see the way in which the mechanism for astra hydrolysis occurs, you have perhaps hydroxide of some sort coming in here, kicking this out, coming back in and giving you this O minus through the tetrahedral intermediate, so it will give you this tetrahedral intermediate which then collapses to kick out RO minus two give you the carboxylic acid right.

Now if you had a serein in the active site doing the same function, then you would get the product and RO minus okay, now because this tetrahedral intermediate collapse is very important, the nature of the living group here in be changed, so for example if you have an electron withdrawing groups such as CH2CF3, then OCH2CF3 versus OCH2CH3 the fluoridated compound is going to be much better living group and therefore it will hydrolyse much faster okay, similarly, you can make other variety of living groups and you can tune the release rates okay.

So the inductive effect of the CF3 is going to make this ester of far better hydrolysing each of the florence are going to have a inductive effect right, so this is going to be far better in kiti-hydrolysed when compare to the ethyl ester.

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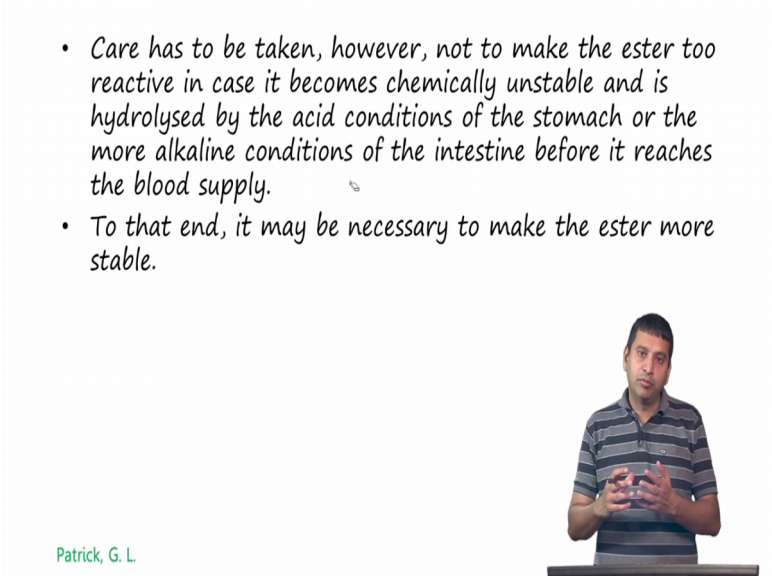

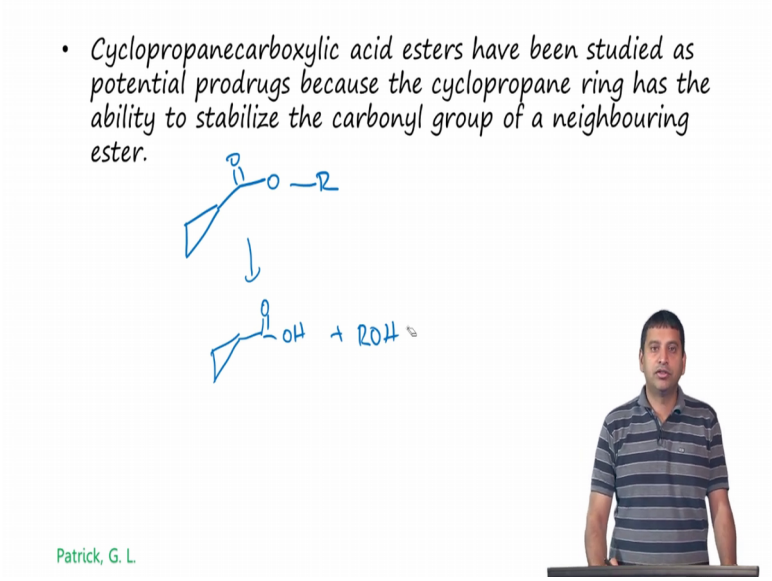

Now of course if you make it too reactive, then what happens is that if the acidic conditions the stomach it can get hydrolysed, you know, almost spontaneously or even in the alkaline conditions that are present in intestine, it can get hydrolysed and that defeats the purpose, so therefore you need to make the ester to be appropriately stable so that it could be hydrolysed in the right rate, in the right place so that it can form the active drug and the right area.

So another example of ester that is a carboxylic acid is the cyclopropanecarboxylic acid esters, so if you over to make, you know imagine that you are drug has an alcohol, so then you could make a cyclopropanecarboxylic acid ester and can again go under hydrolysis to give you cyclopropanecarboxylic acid and ROH okay, so now let us look at this little bit in detail.

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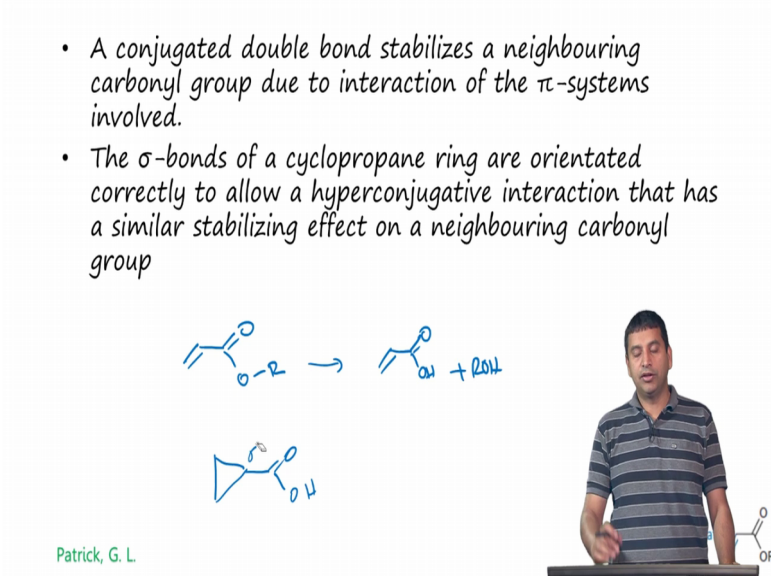

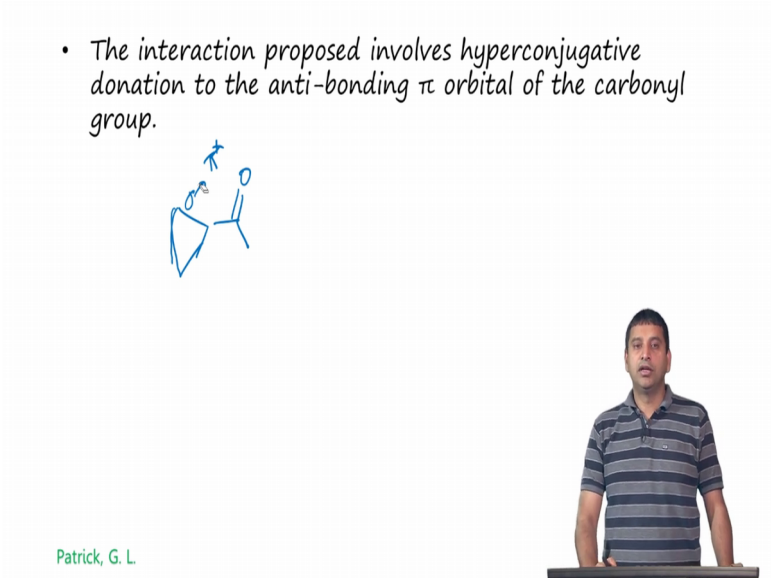

So you can also have a conjugated double bond, so for example can make C double bond O, OR and what is does is that because of the interaction of the pie system, you can now change the way in which the carboxylic acid is going to hydrolysed, so you would get OH plus the product as ROH okay, so similarly, if you compare the conjugated alkane and the cyclopropane, in the cyclopropane the sigma bond of the cyclopropane are oriented correctly to allow for hyperconjugative interaction.

So if you see, so hyperconjugative interaction can occur and this are the sigma bonds and this allows for the conjugation to occur, hyperconjugation to occur and it is going to stabilise the carboxylic acid and of course we know that the hyperconjugative effect is donation to the anti-bonding pie orbital of the carbonyl, so you have a C double bond O and you have a anti-

bonding pie star and here the sigma bond donates to the pie star of the carbonyl and stabilizes it, okay.

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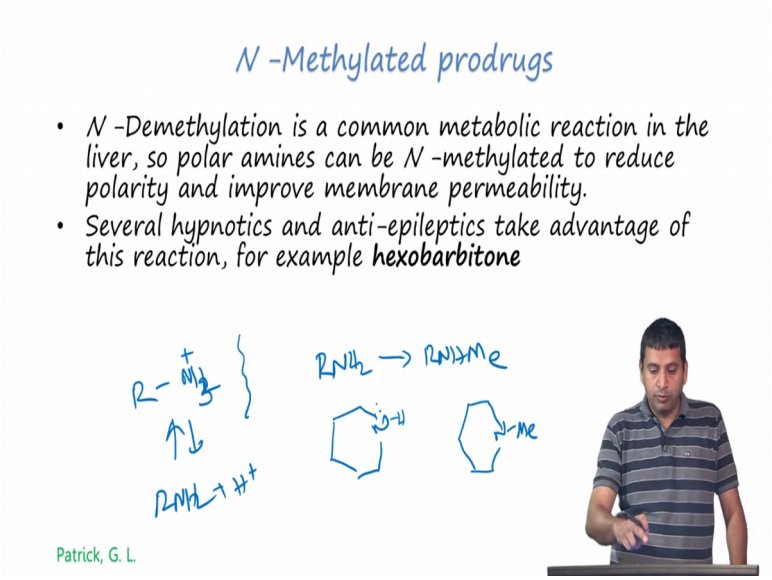

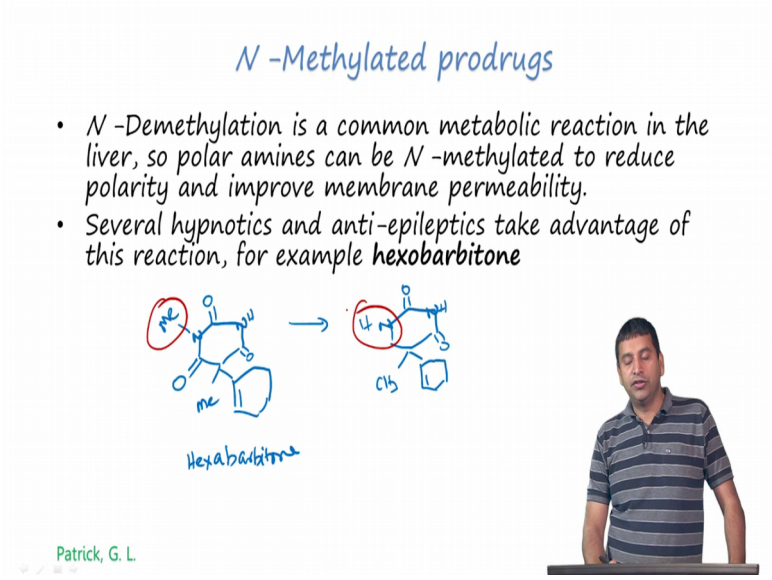

The next way in which you can do this, to make prodrugs is to use N methylated prodrugs, so N demethylation we have looked at previously is actually a way common reaction that occurs and it would produce a polar amine okay, so what we can do is we actually methylated so that you can reduce the polarity and this improves the membrane permeability, so if you see, for example if you have a membrane and you if you have NH2 plus right, which is going to be possibly, you know equilibrating with RMH2.

Now if you can convert, sorry this is NH3 plus and RNH2 and now you can imagine RNH2 being converted to RNHME okay and the position of this equilibrium would be quite

different, similarly, if you had apriline type of ring or pyrrolidine type of ring, if it has NH instead of that if you have NME, so here this lone pair is more available and it is going to get protonated we as the methylated one is not going to be very well protonated due to steric, so there are several examples of this which are known, so what would we do is we would purposefully convert an amine into the methylated amine, so that reduces the polarity and improves the membrane permeability.

So the example that we are going to look at is this molecule, which is hexobarbitone whose structure is shown here and it has a an amine or an amide here and this is hexobarbitone with the methyl group and now it undergoes the metabolism to give you the active derivative, so if you see here the methyl group has been removed and you actually get a NH okay, so this is an example of how demethylation can be used for generating a active drug.

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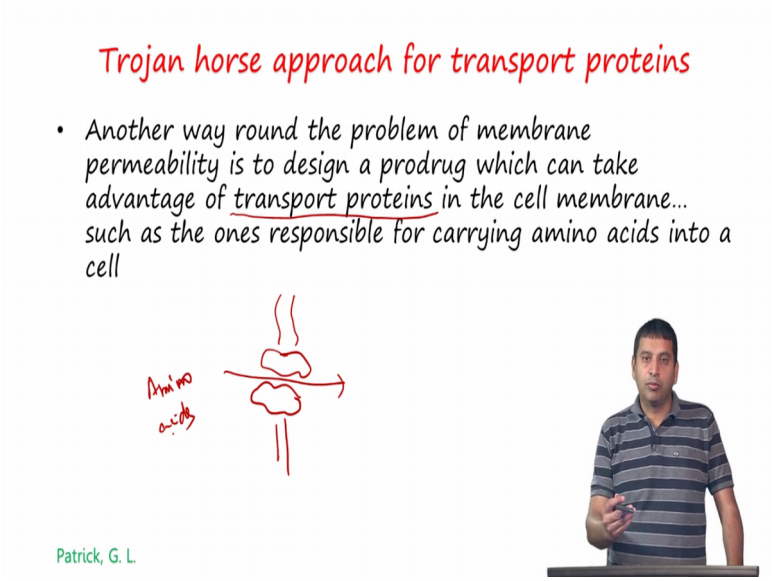

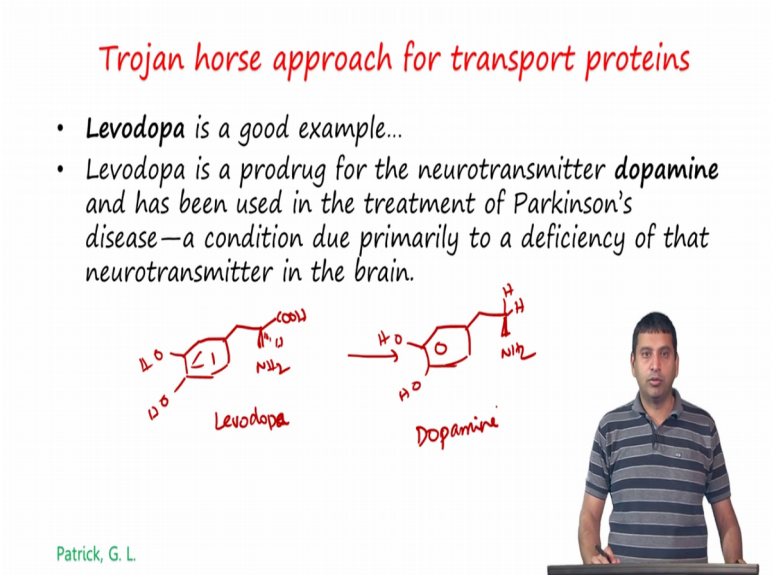

Another major way for prodrug approach is to look at the Trojan horse approach, so one of the major problems with delivering molecules is the permeability of this molecule because we have spent a lot of time in designing molecules which can actually interact with hydrogen bond or ionic interactions and all that and all of these are quite polar, so now for these two get across the membrane is going to be difficult, however there are proteins which are known as transport proteins which you have looked at previously and this are responsible for carrying amino acids into the cell.

So one way to work around the problem of membrane permeability is to use this transport proteins, so here this transport proteins are actually located inside the membrane and they have very much structures like these and these allow for transport of amino acids okay, so the concept would be to be able to use this transport proteins to get across your drug.

Okay, so example that we are looking here is levodopa, so levodopa structure is shown here, we have looked at it previously, it resembles naturally occurring amino acid except that it has two hydroxyl groups and this is levodopa and here is actually inside the cell its get converted to dopamine which we have already looked at previously okay, so this is dopamine right, this is a drug that is used for the treatment of parkinsons diseases and in this disease one of the symptoms of this disease is a deficiency of neurotransmitter yes in the brain .

So the idea would be to deliver this neurotransmitter to the brain right, so levodopa as you can see as a amine as well as a carboxylic acid, so what one could design this prodrugs to be is to actually access the amine as the transporters and get it across cell, once it gets into the cell it gets decarboxylated and produces the active dopamine okay.

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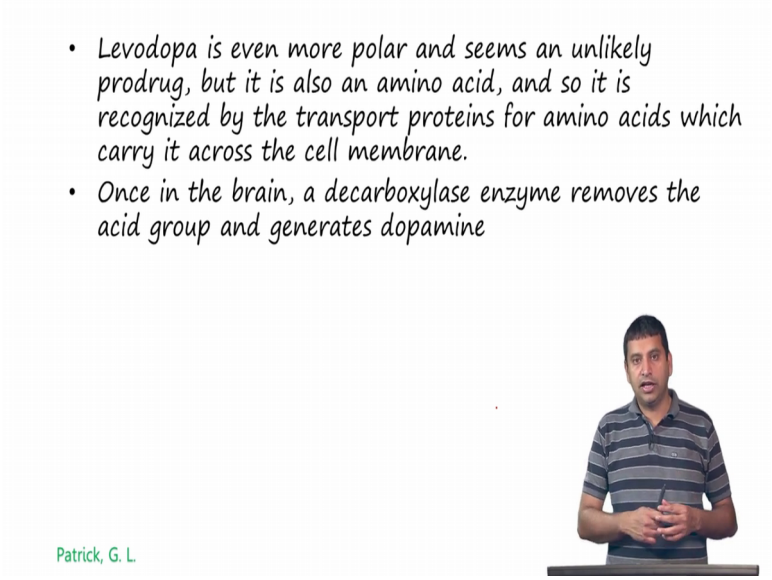

A levodopa is your more polar and since like an unlikely product, but because of its resemblance to an amino acid, it is recognised by transport proteins and it gets across and as we discussed earlier, once it is in the brain a decarboxylase removes the acid group and generates the active dopamine.

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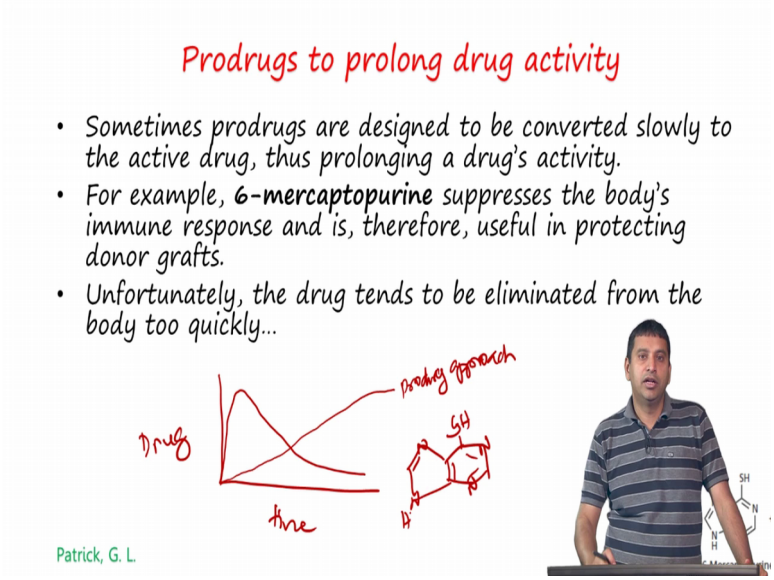

The next concept is to be able to prolong the drug activity okay, so sometimes prodrugs are designed to be converted very slowly into the active drug here the idea is that you know want, for example, that are to be present at very high concentrations the all times, so you want to be able to generate the drug in a slow fashion, so let say we plot the concentration of a drug

versus time, so without a prodrug what happens is that you will have a spike in the drug concentration and then it goes down right.

But imagine if you want to generate this drug for a long time, so then you could masked it is a prodrug, so that it generates active drug over a longer period of time right, so this is one of the important approaches that are used in prodrugs, so the example we have going to look at is the 6 mercaptopurine, so the structure of 6 mercaptopurine is the following, you have a heterocyclic ring N, N double bond and as the name mercapto suggest it should have a sulphur okay, so this 6 mercaptopurine, it has a hydrogen over here and this is a drug that is used to suppress the immune response.

So when you have a transplantation that occurs, the donors organ is given to the acceptors organ and once we have the donor graph that sits inside the body of the acceptors than the person immune system is going to recognize it as a foreign substance and try to get rid of it, so in order to protect it, there are immuno suppressants that are given and 6 mercaptopurine is one of the immuno suppressants.

But the problem with this molecule is that it is get eliminated very quickly in the body, so we want to be able to protect it from metabolism so that it is generated very slowly over a period of time, so that the rejection rate goes down.

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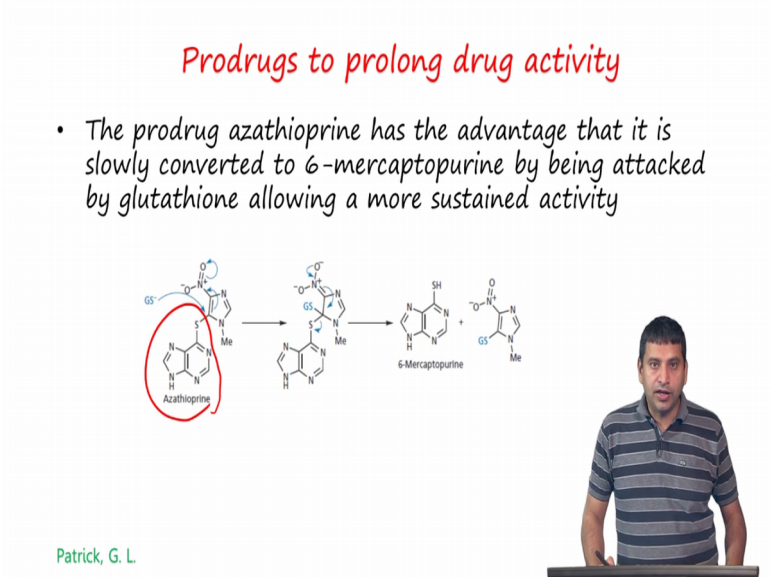

In order to do this, what we do is we convert this molecule into a prodrug okay, so this azathioprine is a prodrug okay, so the concept here is that if you see the structure of mercaptopurine is over here, you protect it with this nitroimidazole molecule, this

nitroimidazole molecule is very interesting because it has a site which is highly electron deficient okay, so this site which is as drawn here separately has a almost like a Michael acceptor kind of system. Okay.

So as you already are all familiar with Michael reaction is addition of a nuclear file to an alpha, beta unsaturated ester, ketone and so on, here your nuclear file which is in this case a thiol attacks here and you can push arrows to get an intermediate like that, now when the intermediate collapses it has a choice of kicking out glutathione or it kicks out mercaptopurine, so when it kicks out mercaptopurine, mercaptopurine is the actual drug, so by allowing for this molecule to be triggered or activated by glutathione, what we achieved is a more sustained activity.

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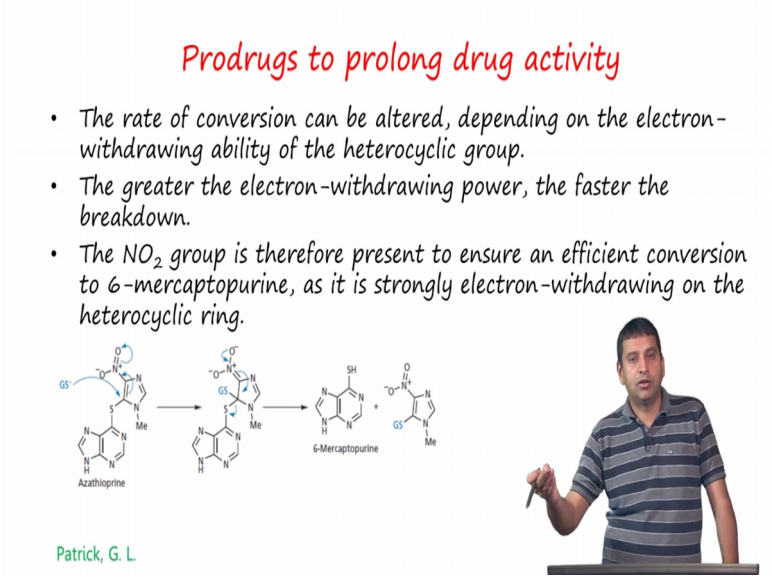

Now what we can do is that we can altered the rate of reaction with glutathione and then you can actually slow down the release further or increase the release, so if you put strongly electron withdrawing group on the imidazole ring, so what we can do is we can actually change the electronics on this ring, so that we can tune the rate of reaction with glutathione, so if we put a strongly electron withdrawing group on this imidazole ring, then you can increase the rate of reaction, whereas if you put an electron donating group and you would suppress the rate of reaction, so based on this one can sort of figure out how the conversion of inactive compound with the active compound in the altered.

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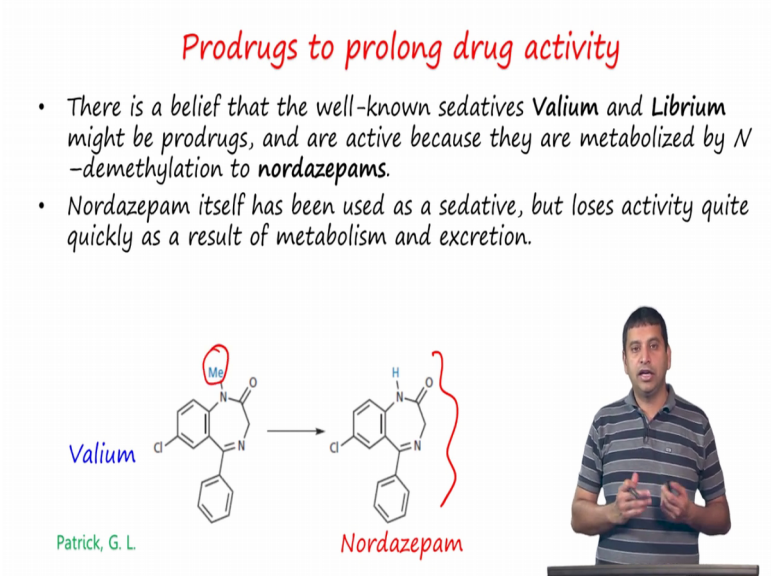

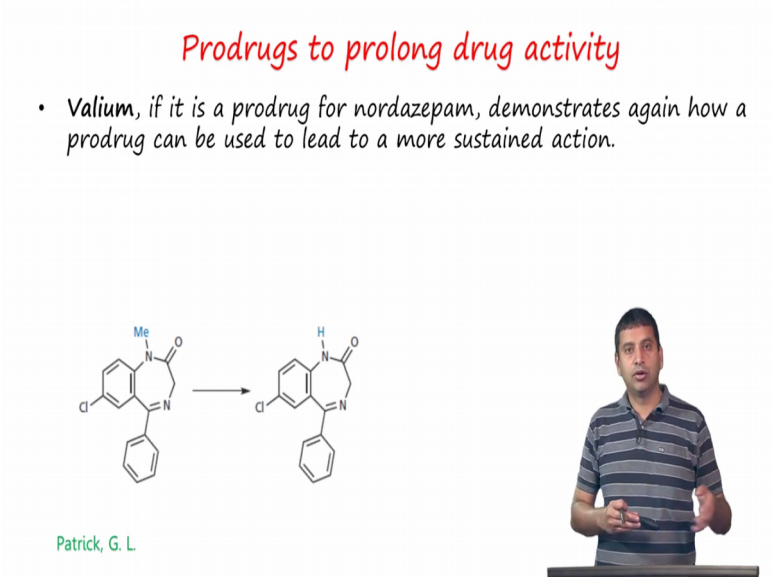

Now there is another commonly used drug which is called as Valium and this is a drug that is used as sedative and it is believed that these sedative such as valium and librium are actually prodrugs and they are metabolized by demethylation to form this active molecule, so nordazepam itself has been used as a sedative but what happens is that it loses activity very quickly because it is metabolized and excreted, so by masking this molecule as valium what happen is that this methyl, N methyl can get cleaved and produced the active compound.

So then what happens is that because it is, it depends on the rate of N methyl demethylation than the activity of this drug can be prolonged, so to lead to sustain action.

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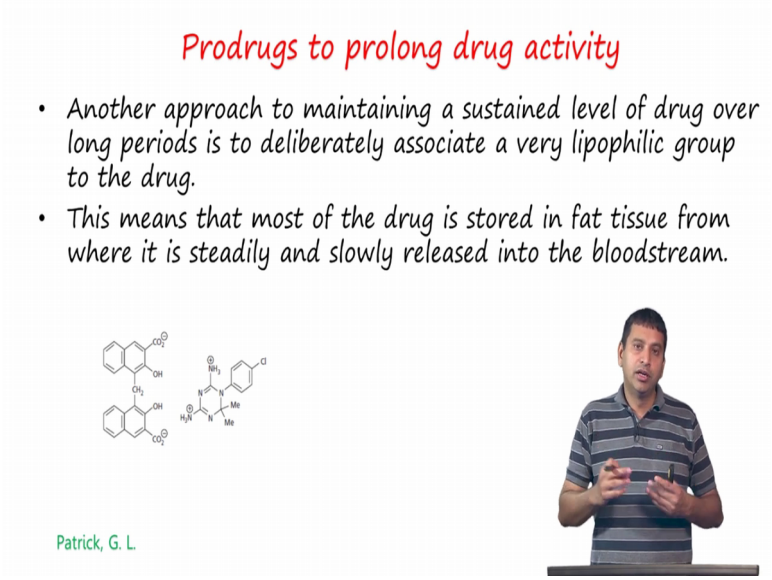

Another approach to maintained a sustained level of the drug is to put in a very lipophilic group on the drug, so this can be done by ionic interaction, so what happens is that the drug will actually because of its close association with this lipophilic group is going to get stored in the fat tissue, so because it stored in the fat tissue it is going to release the drug in a very slow and steady manner into the bloodstream and so this is one of the ways in which you can sustain the release of the drug okay.

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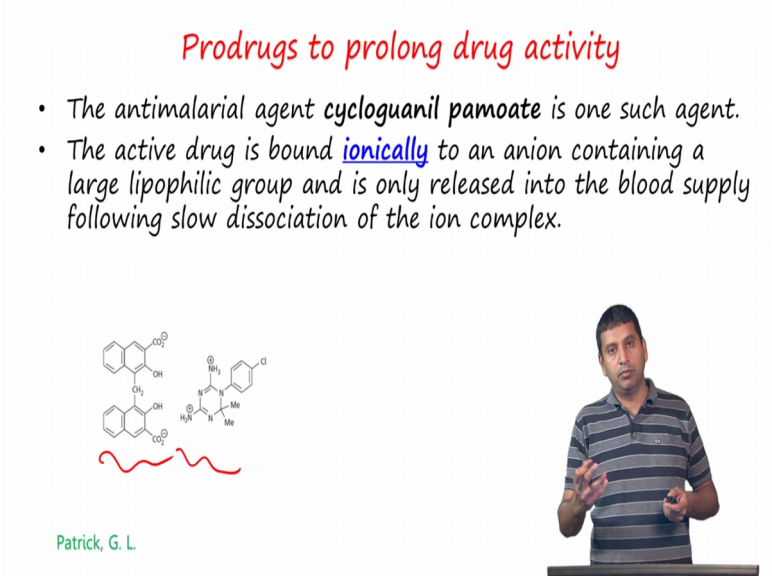

So the example here that we are going to look at is this a antimalarial drug a cycloguanil, so here what we do is that this compound is actually associated with this bis carboxylate shown here and this forms an ionic interaction and this ionic interaction with the large lipophilic

group results in a very slow association of the molecule into the bloodstream and so you can actually regulate the amount of drug that is released into the bloodstream.

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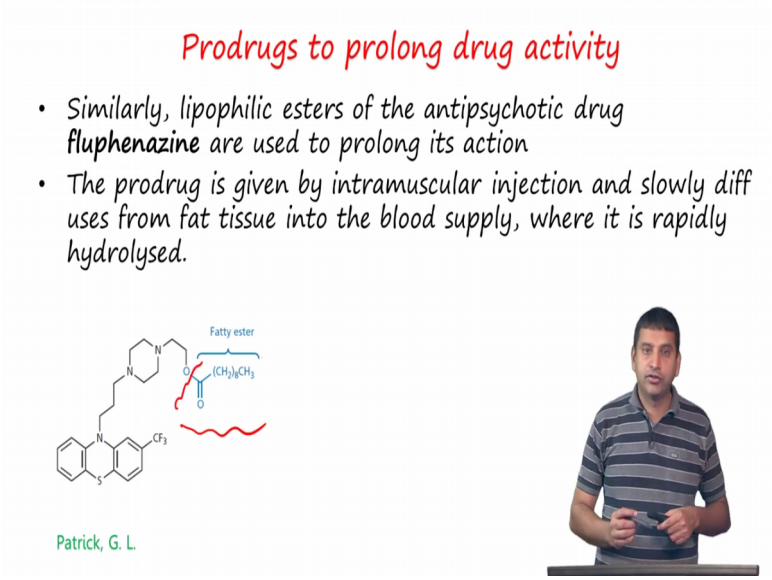

Similarly, you can also use lipophilic esters, so here is a example of a nine carbon appendage which you can use as a carboxylate to your active drug, so the fluphenazine is given intramuscularly and because it has such a large lipophilic group on it a defuses very slowly from the fat tissue into the bloodstream and then once it gets to the bloodstream, it is actually rapidly hydrolysed to produce the active drug.

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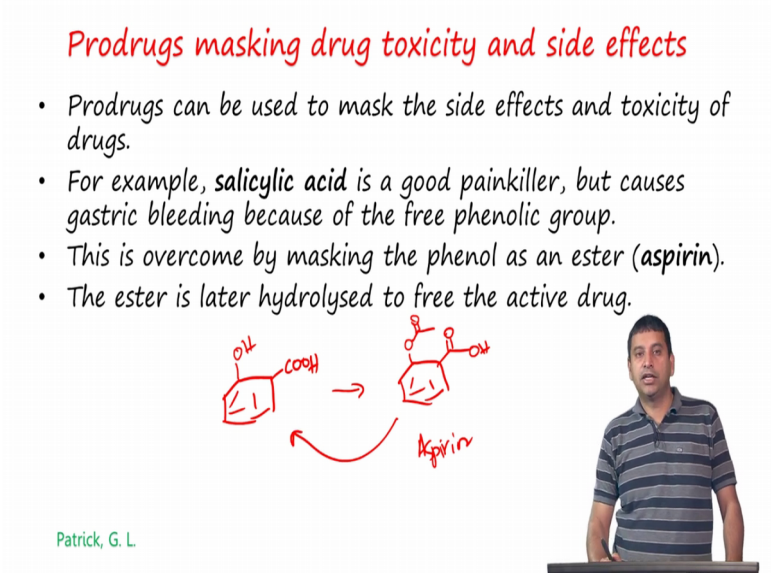

Another major task in prodrugs or major success with prodrugs is to reduce the drug toxicity and side-effects, so for example we all know salicylic acid is an excellent painkiller and once it is consumed in causes gastric bleeding okay, so it is actually converted to aspirin, which is a acetyl salicylic acid, which is basically a prodrug, so this is aspirin okay and so what happens is that aspirin is actually a cleaved within the cell, perhaps by esterases and gives you the active salicylic acid.

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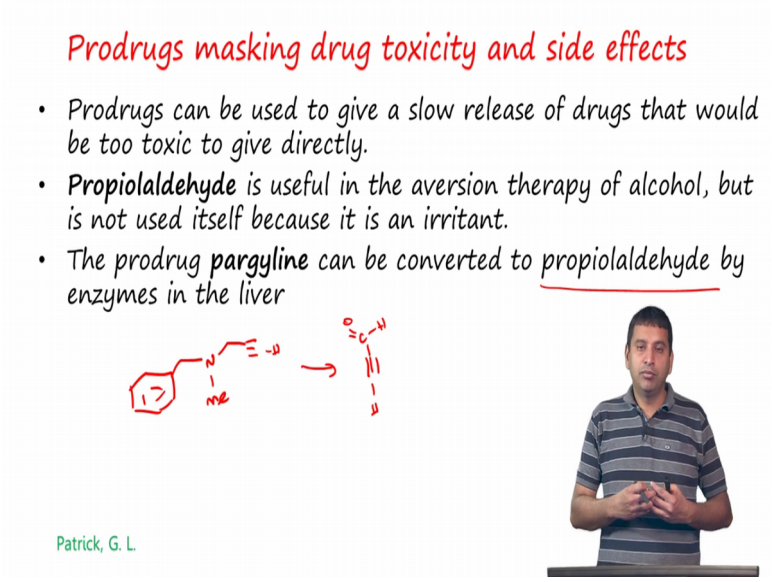

Another way example of this molecule is a propioaldehyde, so the structure of this molecule is as shown here which is NME, it has a propargly group over here okay, so what happens is that this molecule gets cleaved to produce the proparglyaldehyde okay and it is converted to propioaldehyde by enzymes in the liver, so this is one molecule that is given in the treatment of alcoholism, so as you know alcoholism is a situation where somebody who is unable to control the alcohol that they consume, so they are addicted to alcohol and so what happens is that this molecule is given to people and what happen, it creates a very bad taste and therefore it does not now people to orders and help the people to consume alcohol, so it prevents alcohol consumption okay.

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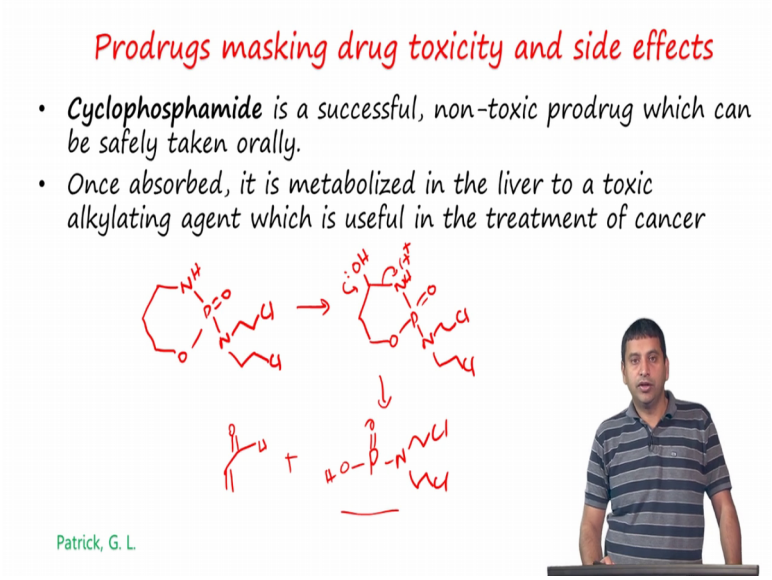

Another classic example of masking drugs is cyclophosphamide, we have already looked at it previously but the concept is very important, so here you have DNA alkylating agent that is masked in the form of a phosphamide and once it gets cleaved it forms the active drug, so here is the position that is susceptible to oxidation and you form. Okay, so now you can think about this going out here and this picking up a proton and giving you this molecule and then subsequently, which will give you the final right and acryline is the byproduct, I will encourage you to push arrows and find the mechanism and so therefore it produces the active DNA alkylating agent and this is used in the treatment of cancer.

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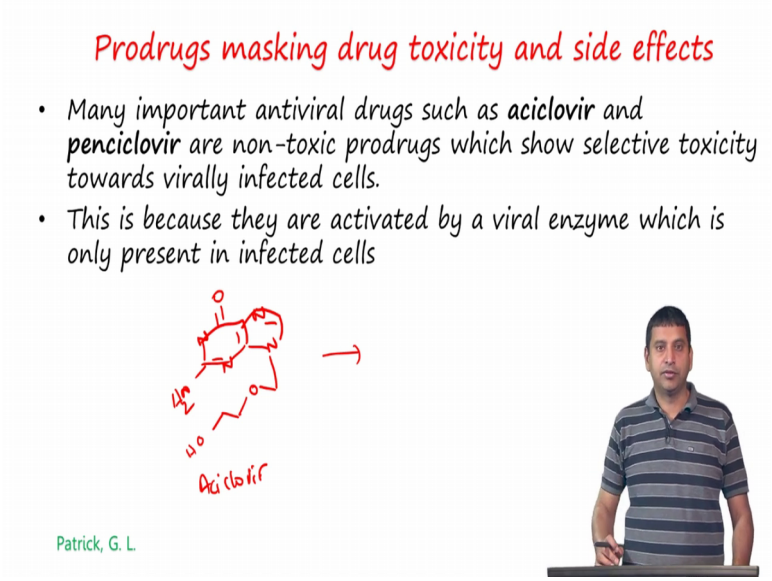

Another example which we have looked at previously are this antiviral drugs such as aciclovir, so aciclovir is a mechanism based inhibitor, so you have, you create this situation where this molecule will go and get, incorporated into DNA but will not allow for replication to occur, so here is the molecule aciclovir right, so what it does is that since it has to be working on viruses, the viral enzyme convert this into an active form and then, only than it can go into an incorporated into the nucleic acid to prevent further replication.