Medicinal Chemistry
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Receptors as Drug Targets Part-2

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So in today's lecture we will continue to discuss the concept of receptors as drug targets. In the last lecture we discussed about how agonist work and how one can understand the various aspects of how agonist can activate a receptor.

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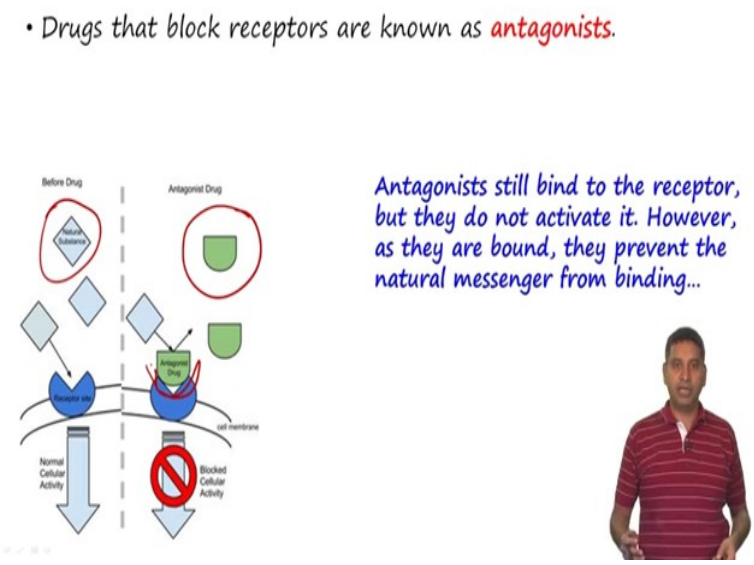

So today we will look at the other concept of antagonist. So antagonists are as the name suggests are molecules which can sort of completely or abrogate the activity of a receptor. So the way we understand antagonist is that. So let us say you have the natural substrate that is binding to the receptor and activating signalling cascade. Now if you have an antagonist drug what it does it goes and binds to the same receptor site and in the process it blocks it. So therefore it is a way in which you can prevent the natural messenger from binding to the receptor.

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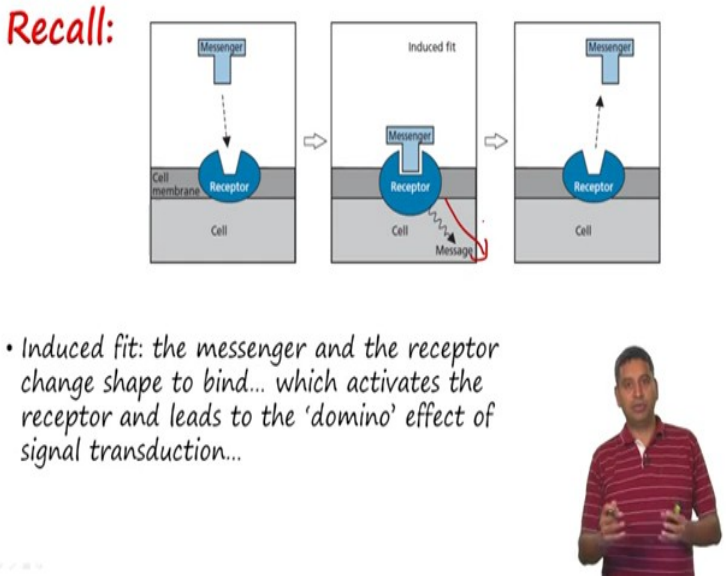

So just to recall the way in which we understand receptor binding is through what is known as the induced fit so the messenger binds and then the receptor undergoes a conformational change along with it the messenger also goes a conformational change and once it binds then the signal is sent forward and after that the messenger dissociates and the receptor goes back to its original shape.

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So now let us look at the principles of an antagonist, how to design an antagonist? And we looked at in the previous lecture, how to design or how to design drugs that can activate the natural receptor I mean activate a receptor to obtain a biological effect. Now what we would need to do in this case is that we would need to figure out how to address a problem, where there are too many messenger molecules acting on the particular receptor. So what happens in this process is that you would have to hyper activation or large scale activation of the receptor which leads to unwanted excess signalling, so we need to design a drug that can counteract this process.

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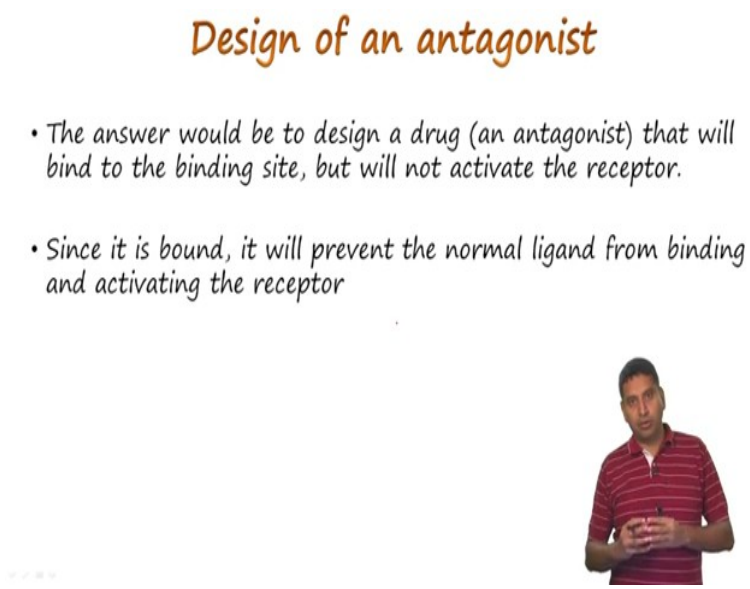

So the answer would be to design an antagonist that will bind to the binding site but will not activate the receptor. Now since it is bound, it will prevent the normal ligand from binding and activating the receptor. So keep in mind we have looked at how enzyme inhibitors can be designed. So for example a competitive inhibitor will go and bind to the enzyme, but there is no turnover. So here in this case an antagonist will similarly bind to the receptor but there would be no signal that is transmitted. So therefore one has to keep in mind this concept while designing an antagonist.

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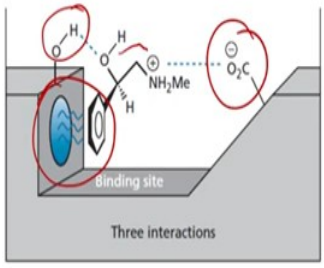

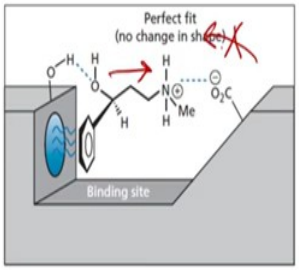

- There are several strategies in designing antagonists, but one way is to design a drug that is the right shape to bind to the receptor binding site, but which either fails to change the shape of the binding site or distorts it in the wrong way.

So there are several strategies which we can employee to design an antagonist, but one of the ways is to design a drug that is in the right shape to the receptor binding site but will either not induce the conformational change or it will distort it in the wrong way. So let us look at this example here, so recall our hypothetical messenger so it had a hydrogen bonding over here and the Van der Walls interaction over here and an ionic interaction over here, so all these three interactions are necessary for the chemical messenger to induce a conformational change to give you the signal.

Now in the case of the antagonist what one could do is if we could elongate this chain a little bit, so keep in mind that this is where the binding happens, but now if you can elongate this chain a little bit, this conformational change that we would expect from here to here may not happen. If that conformational change does not happen then downstream the effects do not occur. So this is one way in which you could design an antagonist. So to recap what we would need to do is to design a molecule that does not induce the conformational change but yet binds to the receptor site.

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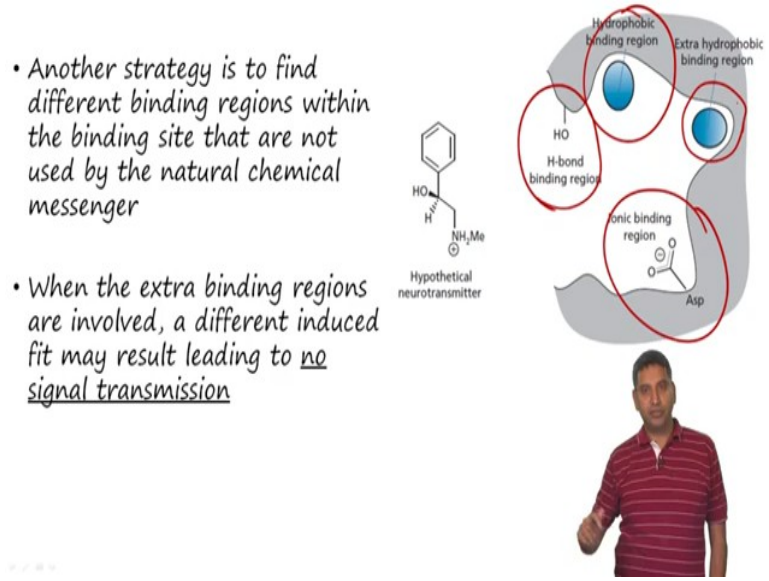

One more strategy is to be able to use binding regions which are not used by the natural chemical messenger. So another strategy is to find different binding regions within the binding site that are not used by the chemical messenger. So recall in our previous hypothetical receptor there was a hydrophobic binding region, there was an ionic binding region and a hydrogen bonding region.

Now all these three are going to bind to the neurotransmitter. However, if you look at the biochemical structure of the receptor you will find that there is an extra hydrophobic region that can potentially be used. Now when the extra binding regions are involved, it may induce a different fit and once this different fit is induced it is possible that that may not be giving out the same conformational change that was necessary for the signal to be generated.

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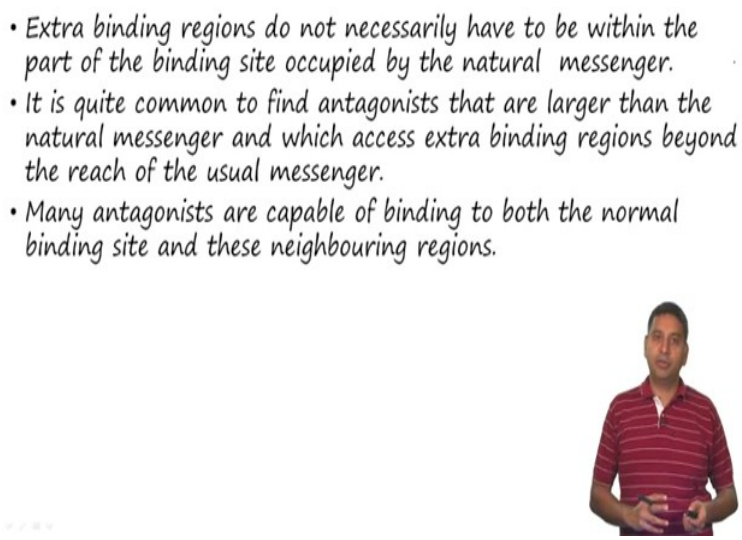

So extra binding regions do not necessarily have to be within the binding site, it could be something that is quite little bit away from the binding site and that can be exploited to design an antagonist. It is also quite common to find antagonist that are larger than the natural messenger, so if they are larger what happens is that they can access extra binding sites beyond the reach of the usual messengers and many antagonist are capable of binding to both the normal binding site and these neighbouring regions that are around this receptor binding site.

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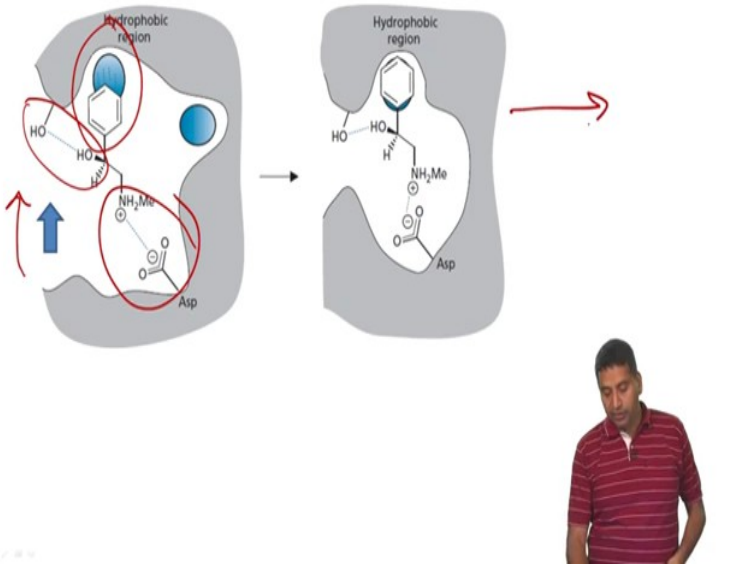

So let us look at this example that we sort of started out with, so here is the natural ligand and what happens is that once it binds to the hydrophobic region and then there is a hydrogen

bonding effect that is here and this is the ionic bond. Now what happens in this process is that this in order to achieve better binding but the pocket moves in and undergoes and in doing so it undergoes a conformational change and this conformational change results in a signal being transmitted.

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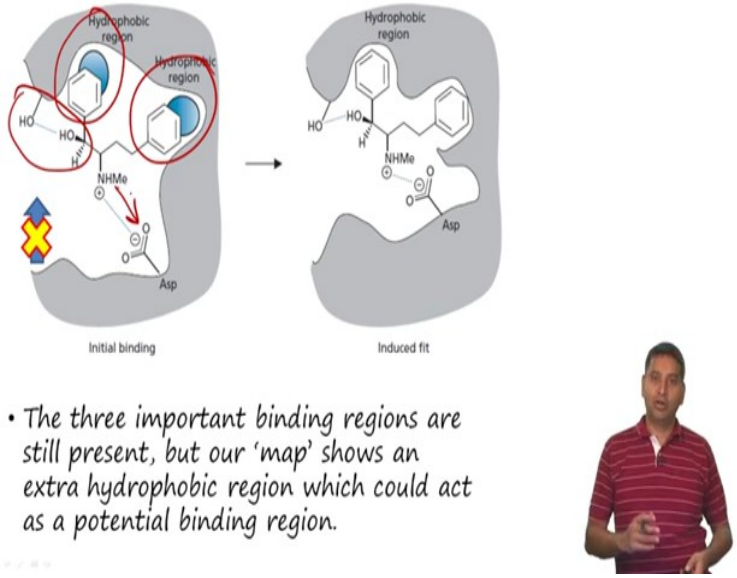

Now if you were to design a molecule that exploited this extra hydrophobic region here, what happens is that the fit of the molecule is such that it binds to the hydrophobic region, it still involves in hydrogen bonding but the only difference is that because it is already bound to the hydrophobic region, this interaction is still happening but does not require the protein to undergo a conformational change.

So the three important binding regions are still present, but the extra hydrophobic region which acts as a potential binding region does not require a conformational change or does not induce a conformational change.

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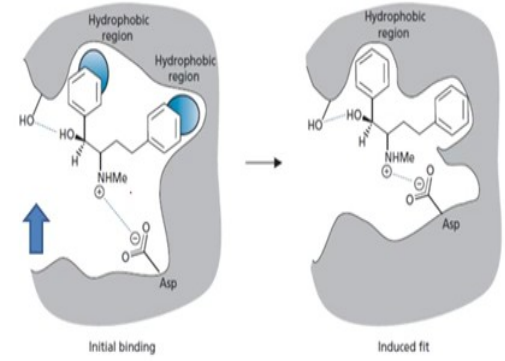

- If the binding produces the same induced fit then we have designed a more potent agonist, but, in this case, the induced fit is significantly different and so the receptor is not activated.

So what happens is that if we have designed a more potent agonist, but in this case since the induced fit is significantly different the receptor is not activated. So this is one principle that one could employ to design a new antagonist.

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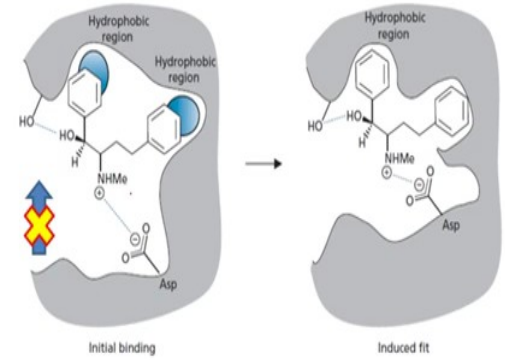

- it binds to the receptor, but fails to activate it. Moreover, by occupying the binding site it prevents the normal messenger from binding.

Now because the antagonist is now bound to the active site or to the binding site of the receptor, it prevents a new molecule a new chemical messenger from coming and binding to it and so because it prevents the new one from binding it acts as a inhibitor or an antagonist.

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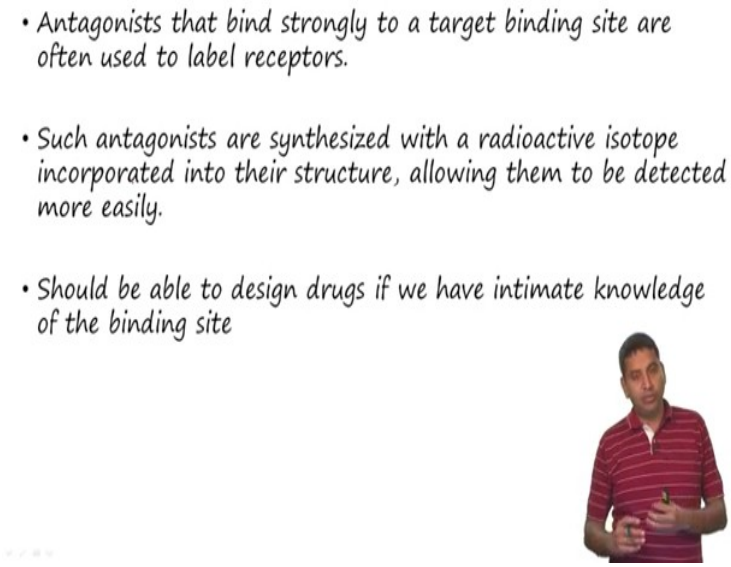

So antagonists that bind strongly to the target binding site are often used to label receptors. So the way we understand the receptor, the topology and the structure inside a receptor is we have to crystalize this molecule in the presence of either the natural ligand or an antagonist. So once we are able to crystalize it then we know what are the kind of interactions that happen inside and we may be able to understand the landscape in the binding site.

Such antagonists are synthesized typically with a radioactive isotope incorporated into the structure, so what this allows us to do is to be able to detect this the presence of this antagonist. So the hypothesis here the working hypothesis here is that we should be able to design drugs if we have intimate knowledge of the binding site which is not easy to attain and it is not as straight forward as it sounds.

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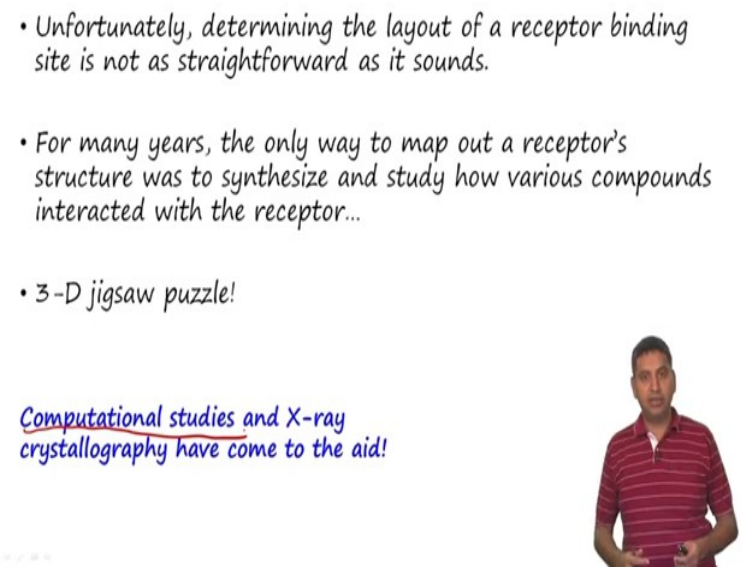

For many years the only way to map out the receptor structure was to synthesize and study various compounds that interacted with this receptor. So we would change the benzene ring to a cyclohexane or put in a substituent in the ortho, meta or para position or change the alcohol to an amine or a carboxylic acid and so on and so forth. So by systematically synthesizing these molecules and studying how they interact with the receptor then what we would be trying to do is to solve a 3-D jigsaw puzzle and we would try and find out where each sort of or what are the various binding sites potential binding sites inside the structure of the receptor.

In the past several decades computational studies have significantly helped because once we have some sort of exercise structure then we would be able to predict what kind of binding sites that are present in the receptor and so on. So these concepts we will look at later in the course.

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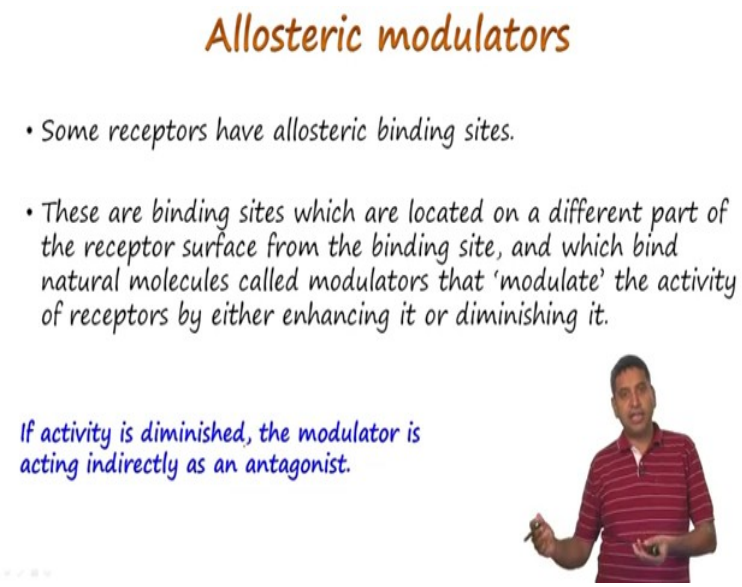

As with enzymes you also have a possibility of allosteric modulation. Some receptors have allosteric binding sites and these are binding sites which are located on a different part of the receptor surface and they bind to the natural molecules called as modulators and these modulators modulate the activity of the receptor by either enhancing or diminishing it. So again one can draw parallel to what we have learnt in enzyme catalysis in that we also have allosteric binding sites which can help regulate the activity of an enzyme. Now if the activity of the receptor is diminished then the modulator is indirectly acting as an antagonist.

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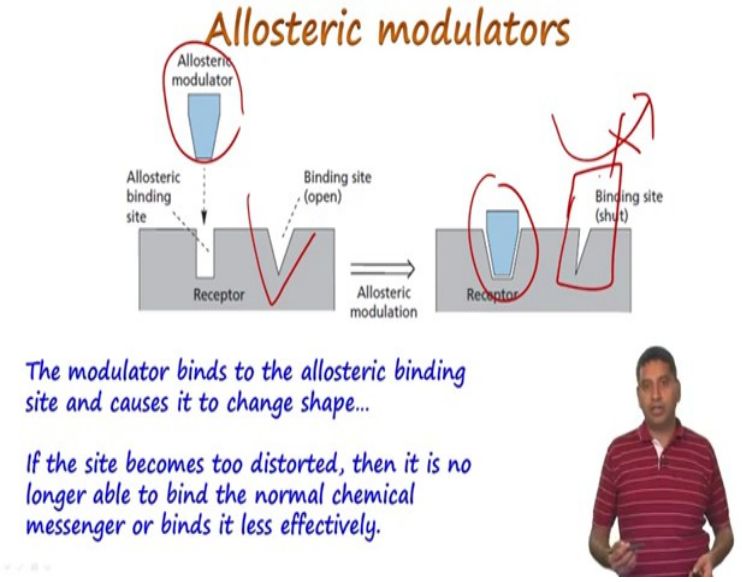

So in order to understand this concept better let us look at a cartoon. So here is an example of an allosteric modulator and here is the binding site for the receptor and once this allosteric

modulator binds this receptor is shut. So again similar to how an enzyme allosteric modulation of an enzyme occurs the main binding site of the receptor is not in play here, it does not directly bind to the modulator, but once the modulator binds to a site which is remote from the binding site, this induces a confrontational change at the binding site which shuts it.

So if the site becomes too distorted, then it is no longer able to bind the normal chemical messenger and therefore there is no activity. So this is how we understand allosteric modulators.

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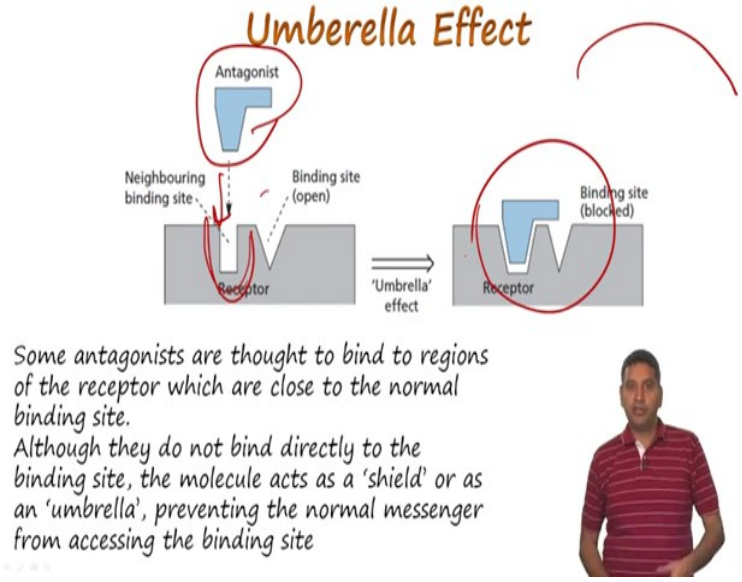

There is also another effect wherein which is called as the umbrella effect. As the name suggest an umbrella can provide shade to an individual, but if it is large enough then it can also provide shade to multiple individuals and so similarly when an antagonist binds to this allosteric site let us say. Now what happens is that it can act as an umbrella and not just provide track with this neighbouring site, it also blocks the binding site. So although they do not bind directly to the binding site this molecule acts as a shield or as an umbrella preventing the normal messenger from acting on the binding site. So this effect is called as the umbrella effect.

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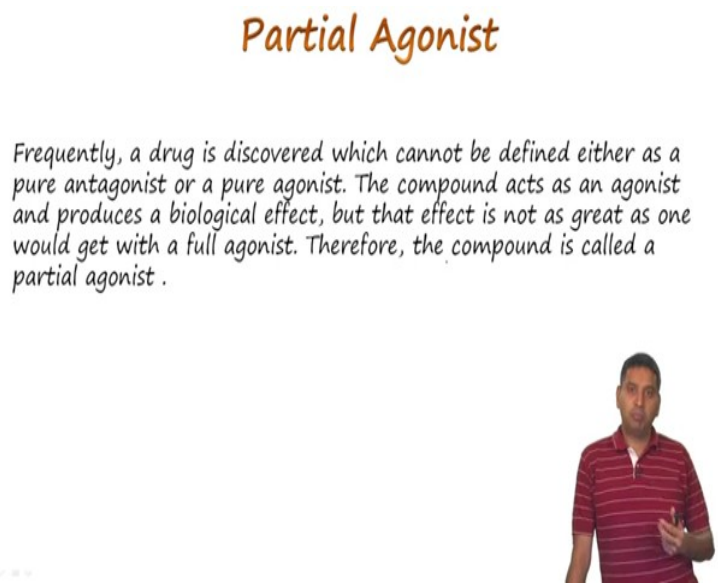

There are frequently when in drug discovery we come across what are molecules which are known as partial agonist. So these are molecules which cannot be defined either as a pure agonist or a pure antagonist. So the compound acts as a agonist and produces a biological effect, but that effect is significantly smaller than what we would get with the normal ligand. So therefore it is called as a partial agonist.

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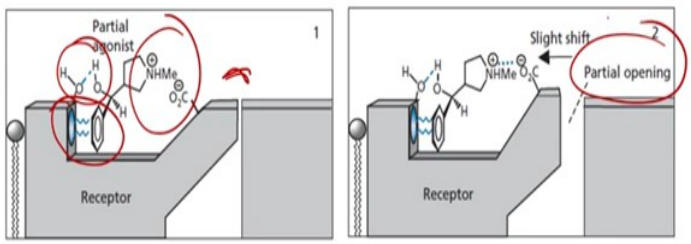

Now let us look at this example over here, so again recall the natural the hypothetical messenger that we used and we have here the same or very similar interactions that are happening, so here is the hydrophobic interaction, here is the hydrogen bonding and here is

the ionic effect. So once this molecule binds to the receptor site, this channel which was blocked is now opened but it is not completely open, so it results in some partial opening.

So imagine that this is an ion channel receptor, so once it binds to the receptor it can open it but which will permit the entry of ions, but it is not completely open, so therefore it is restricted entry into the cell. So what happens is that the rate out at which the signal is transmitted could go down. So this is known as a partial agonist.

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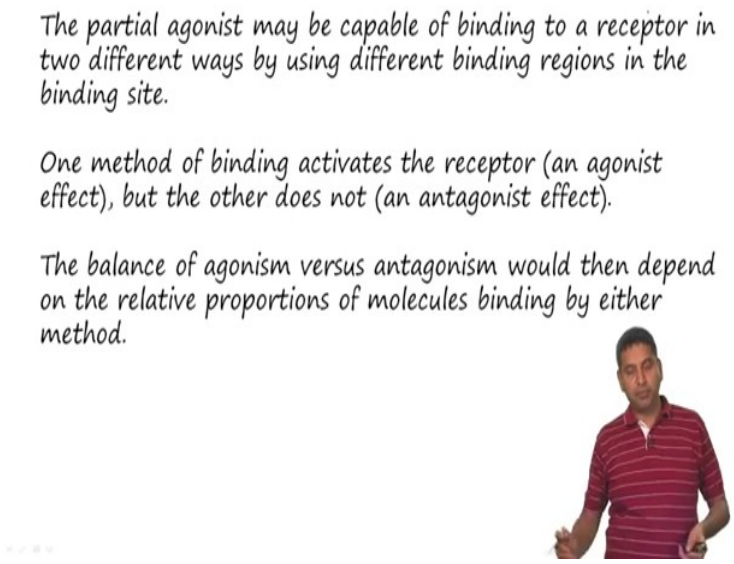

The partial agonist may be capable of binding to a receptor in two different ways by using different binding regions in the binding site. One method of binding activates a receptor that is called an agonist effect, but the other does not which is called the antagonist effect. So the balance of agonism versus antagonism would then depend on the relative proportions of molecules binding by either method. So we will look at later in the lecture how we can understand this by some certain plots.

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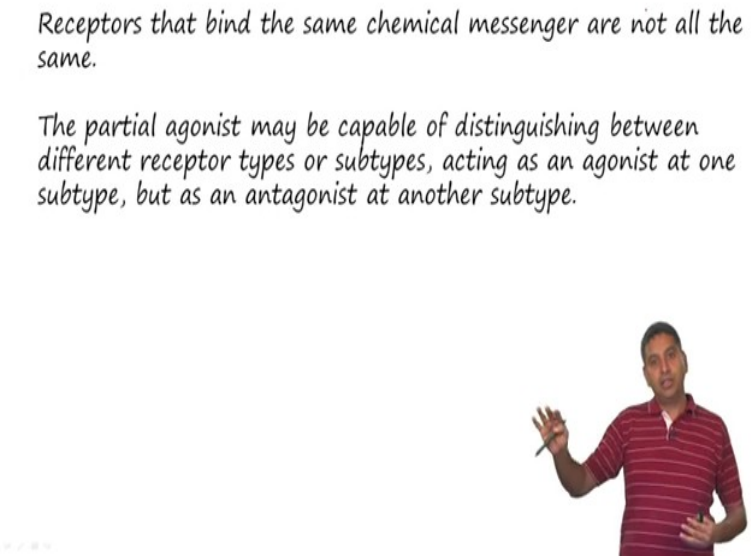

Receptors that bind the same chemical messenger are not all the same. The partial agonist may be capable of distinguish between different receptor types or subtypes. So for example we looked at earlier how a particular receptor in the heart may be structurally different from a particular receptor in the lung and that receptor because of its certain differences can bind to a partial agonist in a way that is very different from the other receptor.

So in doing so what may happen is that the partial agonist may work better on one receptor subtype compared to the other that is it can act as an antagonist for a particular receptor or it can act as a agonist for a particular receptor while it can have a different activity on the same receptor subtype.

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Now let us look at how to understand these drug receptor interactions better? So in order for us to appreciate the mechanisms of drug action, it is important for us to understand the forces of interaction that bind these drugs to their receptors. Again we have looked at in detail the various forms of non-covalent interactions but just to recap you can have hydrogen bonding, you can have dipole-dipole interactions, you can have ionic interactions, you could have hydrophobic interactions, you can have Van der Waals interactions and so on and so forth.

Of course there are covalent interactions which we will not come across very frequently in drug receptor interactions but these non-covalent interactions will play a big role. Now because of the low concentrations of drugs and receptors in the bloodstream, the law of mass action alone cannot account for the ability of how small doses of these specific drugs elicit such a large difference in biological system. So what we need to understand is how this amplification effect happens.

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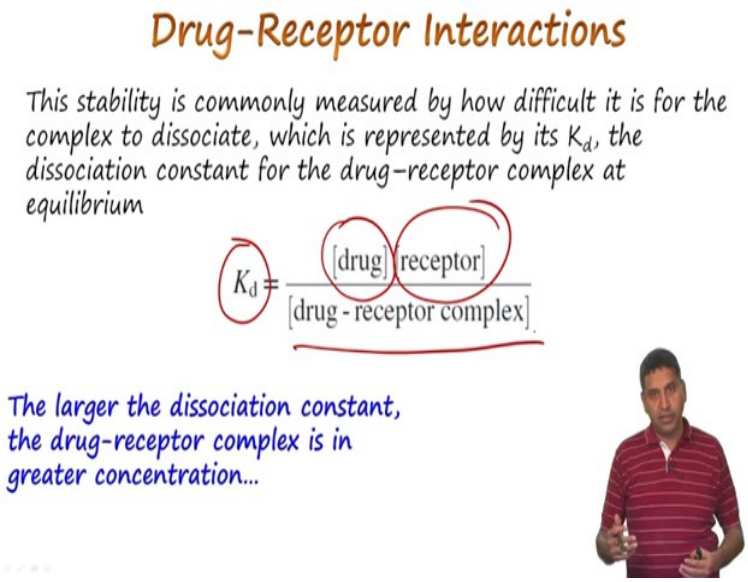

So in order to understand that let us define certain terms now. So the stability is usually defined by an equilibrium constant which we shall call as K_d which is known as the dissociation constant of the drug receptor complex. Dissociation constant is defined as the concentration of the drug here, multiplied by the concentration of the receptor divided by the drug receptor complex. So very simply the larger the dissociation constant, the drug receptor complex is going to be in a greater concentration.

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$$K_d = \frac{[\text{drug}]\,[\text{receptor}]}{[\text{drug - receptor complex}]}$$

The larger the dissociation constant, the drug-receptor complex is in greater concentration... which also means that the drug has high affinity for the receptor!

The median dissociation constant for inhibitor drugs in the market is 20 nM

Let us now look at the factors that determine the drug-receptor affinity...

Now which also means that the drug has a very high affinity for the receptor, so typically large number of study show that the median dissociation constant for inhibitor drugs in the market is around 20 nano molar, so we have molar divided by a thousand you get mili molar and then again divide by another thousand you get micro molar and then divide that by another thousand you get nano molar, so nano molar is extremely small concentrations inside the body. Now let us this for the inhibitor to act at this low concentration we need to understand the factors that determine the drug receptor affinity.

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$$\Delta G^0 = -RT \ln K_{eq}$$

The spontaneous formation of a bond between atoms occurs with a decrease in free energy, that is, a non-covalent bond will occur only when there is a negative ΔG, which is the sum of an enthalpic term (ΔH) and an entropic term ($-T\Delta S$).

So as we have studied previously the free energy is related to the equilibrium constant in the following way, delta G not equals minus RT ln K_{eq}, so the spontaneous formation of a bond

that is here a non-covalent bond results in the decrease in the free energy and will occur only when there is a negative free energy of interaction and this negative delta G is related to the enthalpic term as well as the entropic term. So that is we have already familiar with delta G equals delta H minus T delta S.

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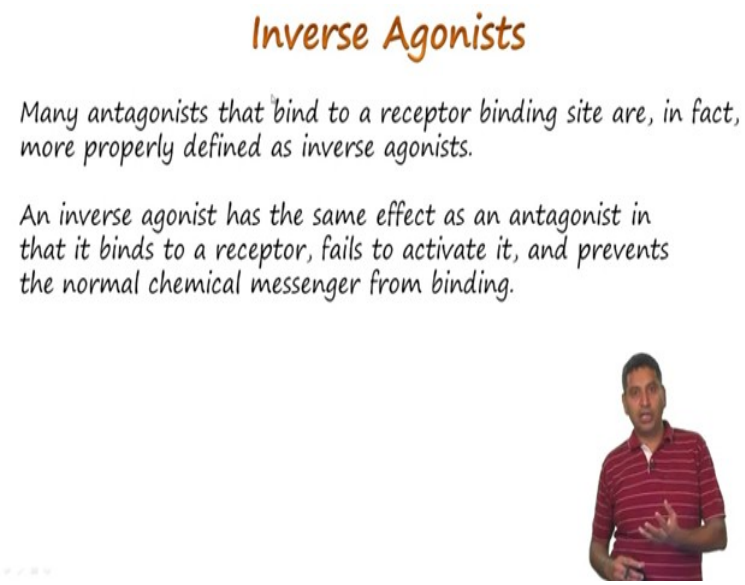

So with this background now let us look at inverse agonists. So many antagonists that bind to a receptor binding site are in fact more properly defined as inverse agonist. So this inverse agonist has the same effect as an antagonist but it fails to activate it. So what this means is that there is some residual activity that is there in the receptor to begin with and this is going to be modulated by the inverse agonist.

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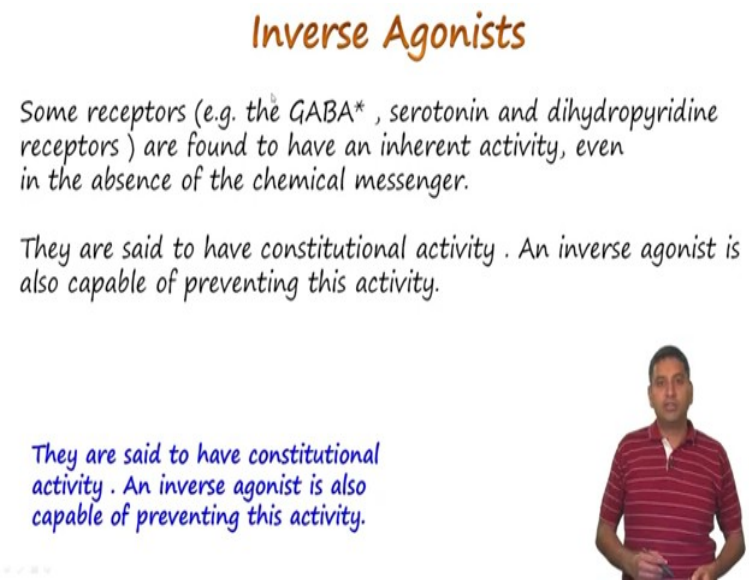

So this was a very important finding because what we have been able to understand from this is that the receptors have constitutional activity and an inverse agonist is capable of preventing this activity. So there are some receptors such as GABA which is gamma aminobutyric acid, receptor serotonin, dihydropyridine receptors which have a low level of inherent activity even in the absence of chemical messenger.

So that means that these are constitutional activities that is already going on inside the cell. Now what an inverse agonist does is that once it binds it prevents the activity from happening. So again we will look at this later in the course.

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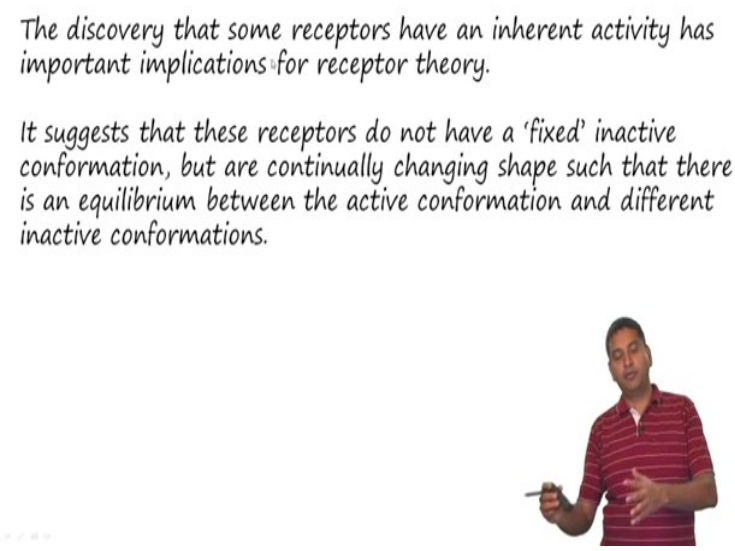

So the discovery that some receptors have an inherent activity has some important implications in receptor theory. It suggests that these receptors do not have a fixed inactive conformation, but are continually changing shape such that there is an equilibrium between the active conformation and the different inactive conformations.

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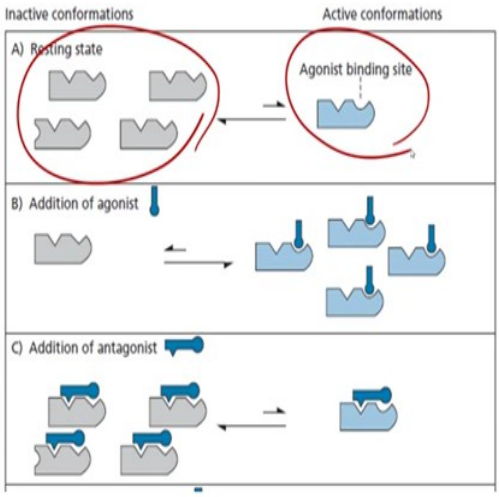

Now in order to understand this let us look at some cartoons. So in a traditional receptor there is a resting state which is shown by these grey pictures here. Now what happens is that it is an equilibrium with the active conformation which is what our inverse agonist tells us.

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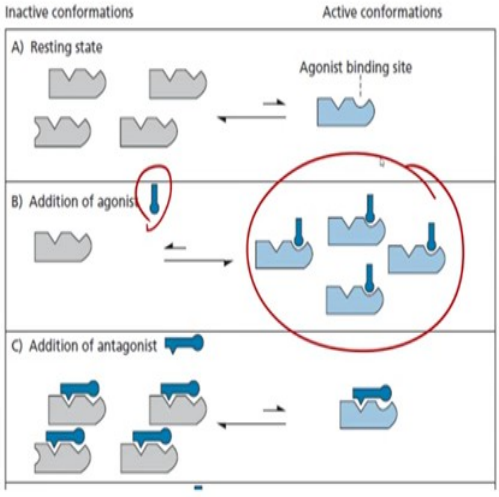

And once you add an agonist what happens is that you have the active conformation in a larger concentration. So once the active conformation is in a larger concentration it results in enhanced signal transmission.

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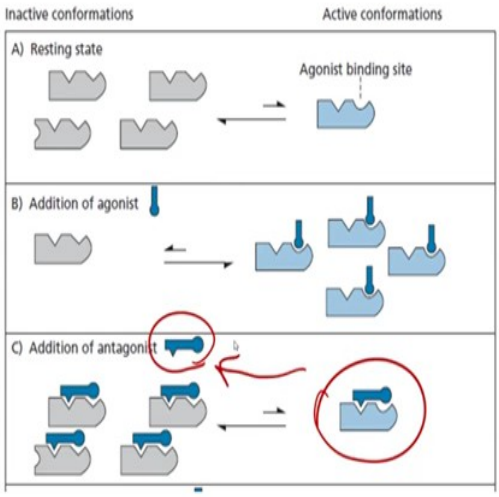

Similarly when you add an antagonist, so this antagonist that is added here goes and binds to the both the active as well as the inactive conformation and once it bind to the active conformation it pushes the equilibrium in the direction of the inactive conformation and therefore the signal goes down.

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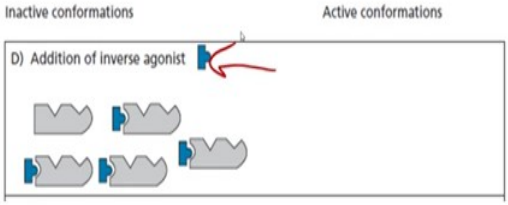

An inverse agonist is proposed to have a binding preference for an inactive conformation.

This stabilizes the inactive conformation and shift s the equilibrium away from the active conformation leading to a drop in inherent biological activity

An inverse agonist is proposed to have a binding preference for the inactive conformation and once it stabilizes the inactive conformation it shifts the equilibrium away from the active conformation so therefore there is a drop in the biological activity.

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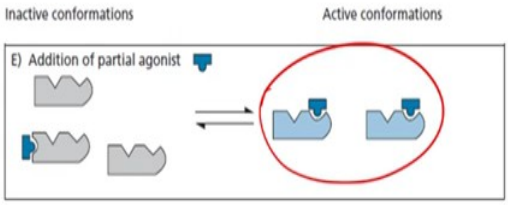

We looked at the concept of a partial agonist and in order to understand this what we can we can again propose an equilibrium between the active and the inactive conformations and the partial agonist binds to the active conformations as well as the inactive conformation and what it does is that it allows for this equilibrium to occur wherein only a diminished signal is manifested.