Medicinal Chemistry
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Module 02 Lecture 10
Introduction to Receptors

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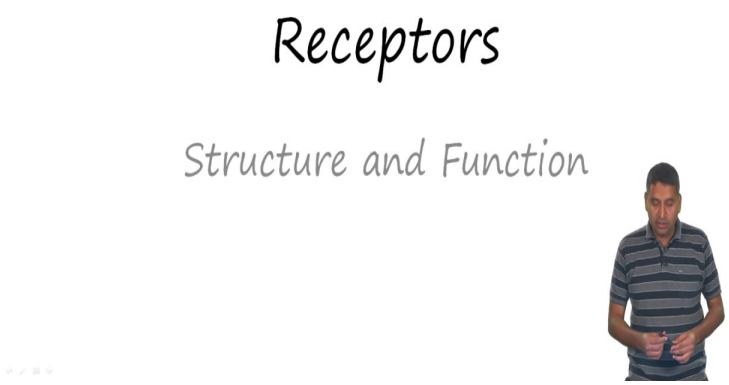

Welcome back, so in today's lecture we will look at receptors. We will focus on understanding mainly the structure (and how) structures of the receptors and how they function ok.

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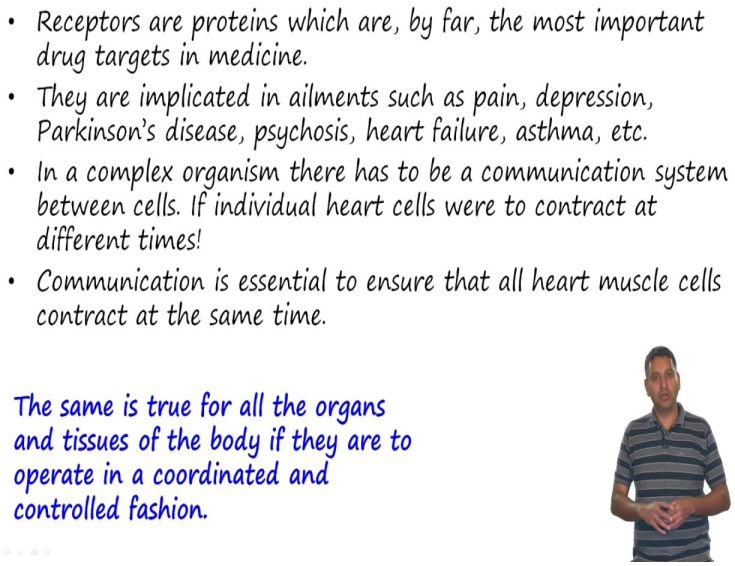

So receptors are we discussed earlier are very important proteins which are by far the best the most important targets in medicinal chemistry and a number of diseases that we suffer from are related to receptors. So for example pain, depression, in some cases heart failure, asthma and some certain neurodegenerative disorder so all in some way shape or form connected to the dysfunction in receptors. So in a to understand this one needs to understand how communication system works between cells especially in a complex organism.

So if for example there are individual heart cells and each of this heart cell is going to contract lets say at different times ok, so then it would lead really lead to a chaotic system. So one needs to make sure that the communication within and among these heart cells occurs in a very efficient manner so that all the heart cells contract at the same time. So that the blood can be circulated efficiently ok.

So using this similar concept it is true for one can extrapolate this to the other organs as well. So all the organs have a coordinated function and this need to be controlled and receptors are the ones which are responsible for this kind of coordination and control ok.

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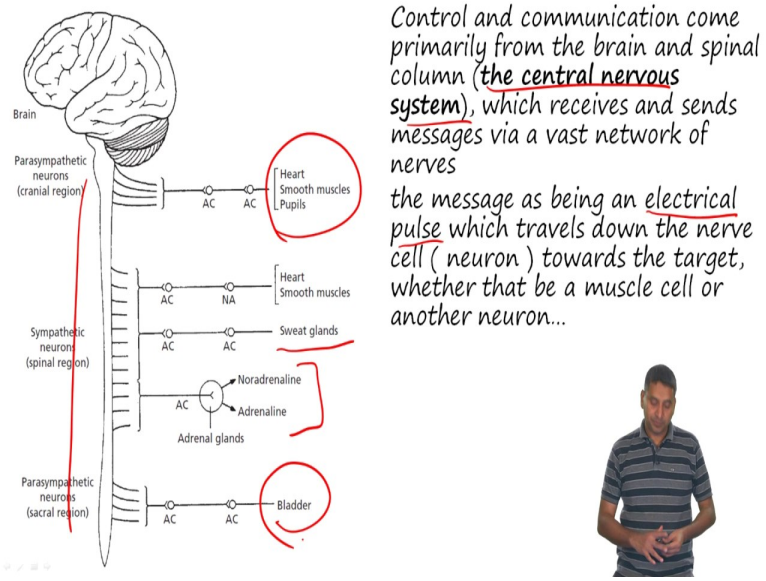

So and a lot of the coordination in communication system originates in the brain ok. So here is a schematic of the brain and which what we call as a central nervous system and offcourse there is a spinal cord and all of this contain neurons ok. So these are the ones that generate the signal and transmit it ok. The signal that we are talking about is nothing but an electric pulse, so this electric pulse travels down the nerve which is also called the neuron towards a target right and so it communicates to the target whether let's say a muscle should contract or not.

From the brain a lot of this signals transmit and they control the functioning of the heart, smooth muscles, the pupils for example and then we also have the signal controlling how certain glands work and so does for example the adrenal glands or sweat glands and offcourse you know including the excretory system is controlled by this types of signals ok.

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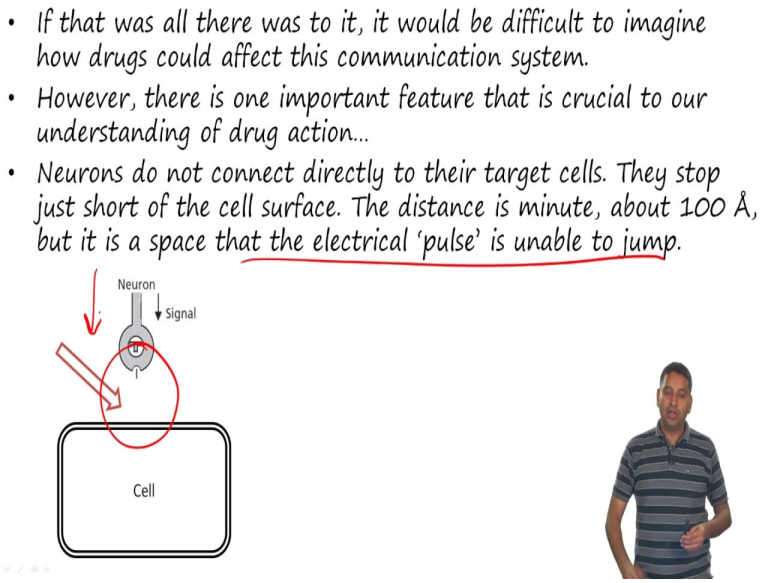

Now if offcourse if it is all that there was to signaling it would be difficult to imagine how this drugs can actually affect this communication system? So what is the important feature that is crucial to the understanding of how drugs work on receptors is that these systems are not directly connected ok. So for example, neurons do not connect directly to the target cells, there is just a small distance typically may be of 100 Angstrom where in there is a gap ok. So this distance this gap has to be covered which the electrical pulse is unable to jump.

So what happens is that the signal gets all the way here and then its stops.

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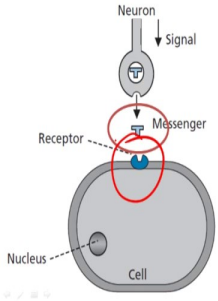
- The problem is solved by the release of a chemical messenger called a neurotransmitter from the nerve cell.
- Once released, this **chemical messenger** diffuses across the gap to the target cell, where it binds and interacts with a specific protein (receptor) embedded in the cell membrane.



So the way in which this is further transmitted is through small chemical messengers, these are known as neurotransmitters and this originates from the nerve cell ok. So what happens is that the messenger travels that distance from the neurons to the target and there is an across this gap and then interacts with the specific protein or a receptor that is on the surface and then there is a signal that is given out ok. So these chemical messengers which are known as neurotransmitters are primarily responsible for the signal that is transmitted.

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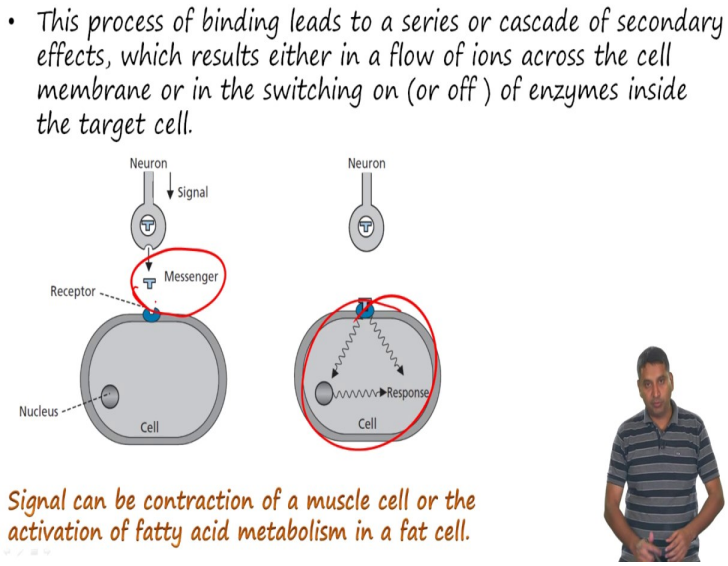

Ok, now what happens is that, after the binding of the messenger to the target occurs it results in a cascade of secondary effects ok, so what these effects are could be for example, few of ions which result in the changing in the ion the potential inside a cell or it could be switching on or off an enzyme inside the target cell. So for example, the signal of can be like contraction of a muscle cell or it can also be metabolism which terms of stress where the fatty acids metabolism is signaled in a fat cell ok.

So this signal that is being transmitted occurs within the cell, so to recap the neuron has an electrical impulse which is then transmitted upto a particular point after which a messenger which is usually a small molecule carries that signal forward to the site of interest wherein receptor interacts with this messenger to transmit a signal ok.

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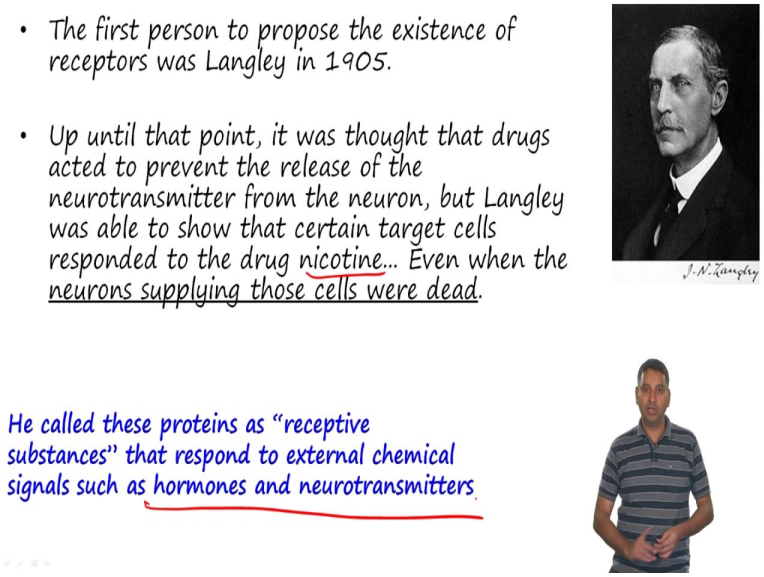

The first person to propose the existence of receptors was Langley ok, what he did was he conducted an experiment wherein he was able to show that certain target cells responded to a chemical neurotransmitter which is a nicotine even when the neurons that were supplying this cells were dead. So what it means is that, you need he could figure out or he demonstrated that it is a chemical messenger which interacts with the target, second thing is that he also showed that there is a target which responds to chemical messengers ok.

So these proteins are he coined the term as receptive substances which are now called as receptors and they respond to this chemical signals which are now broadly two classes which is hormones or neurotransmitters.

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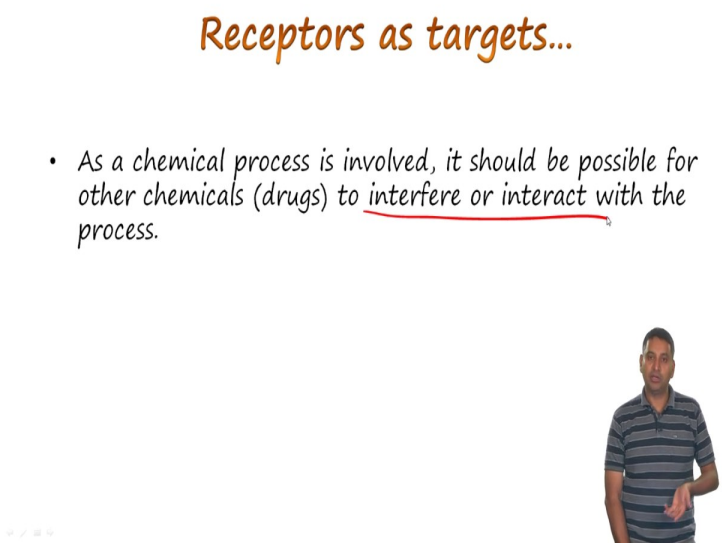

Ok, so when there is a chemical process that is involved it is logical for us to propose that other chemicals such as drugs can interfere or interact with this process and therefore receptors can be good targets for drug discovery.

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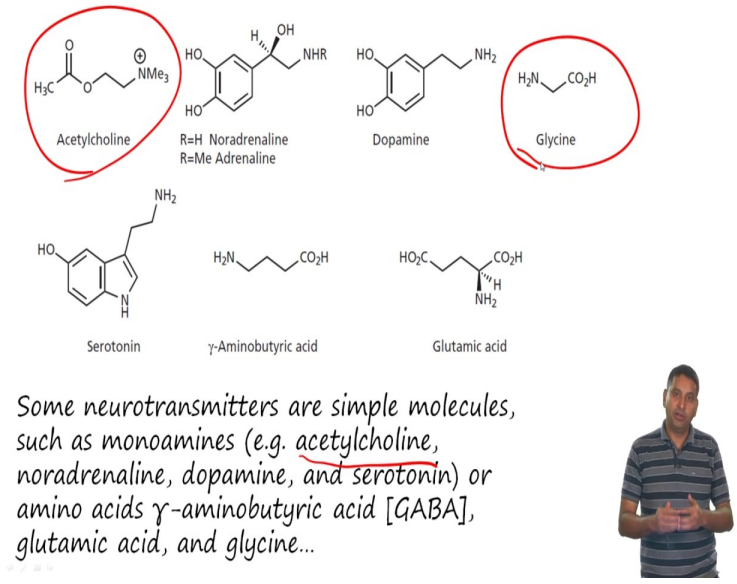

So if you look at the structures of some of the neurotransmitters you will find that many of them are simple molecules such as monoamines, an example is acetylcholine whose structure is shown here, it is a very simple small molecule has an amine which is positively charged ok. There are

other examples such as Dopamine or Noradrenaline and even simple amino acid called as a Glycine or Gamma-Aminobutyric acid, Serotonin acid and Glutamic acid.

So these are some examples of neurotransmitters which help in transmitting a signal from a neuron to the target cell.

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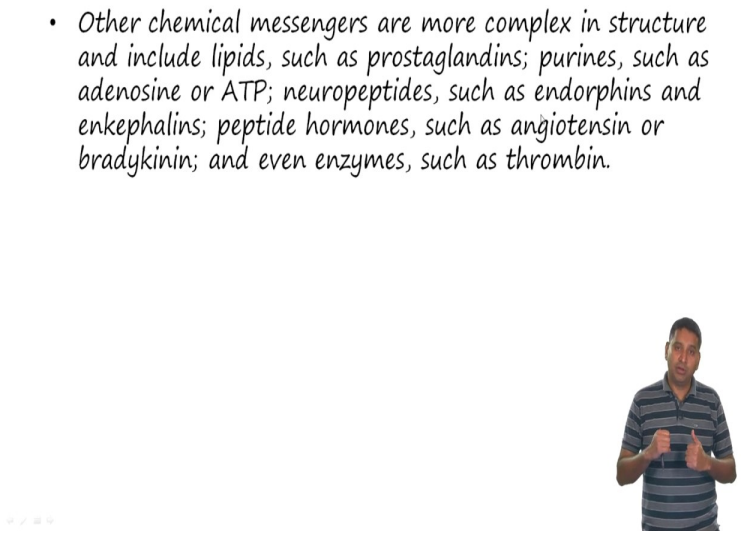

You can also have fairly complex structures such as lipids, examples are prostaglandins or purines such as adenosine or ATP and sometime you can also have neuropeptides such as endorphins which can transmit the signals. Other examples are also peptide based hormones such as angiotensin or bradykinin and even sometimes enzymes can do this play this role of transmitting signals ok.

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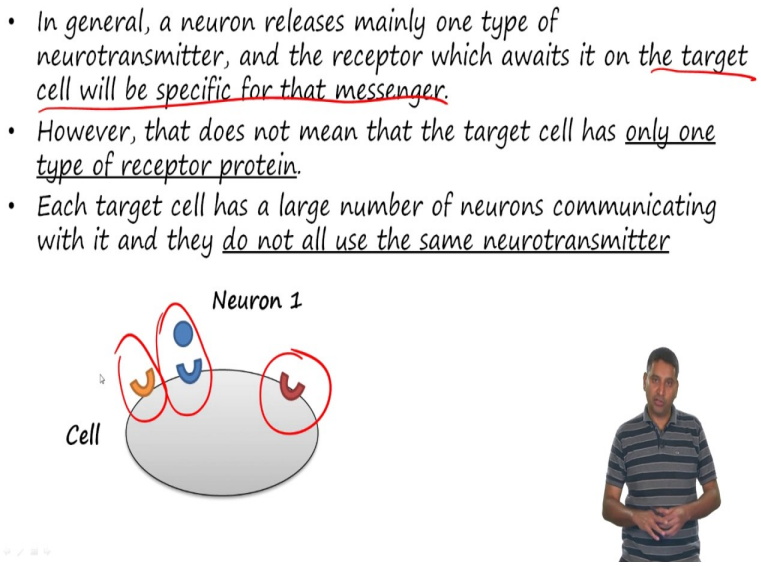

In general a neuron releases mainly one type of neurotransmitter ok and the receptor which is present on the target cell waits or responds for this signal to be to arrive ok, or this neurotransmitter to arrive ok. So the target cell is specific or there is specificity in the target cell for the messenger. However it does not mean that the target cell has only one type of receptor, so in this schematic so here is a target cell and here is one of the neurons that is generating this neurotransmitter which I am showing in blue to the receptor which I am again showing in blue.

But this is not the only receptor that is present in the cell we also have couple of other receptors that I have shown here. Each target cell has a large number of neurons communicating with it and offcourse they don't all use the same type of neurotransmitter and each of the cell each cell has large number of receptors which can communicate with different types of neurotransmitters ok.

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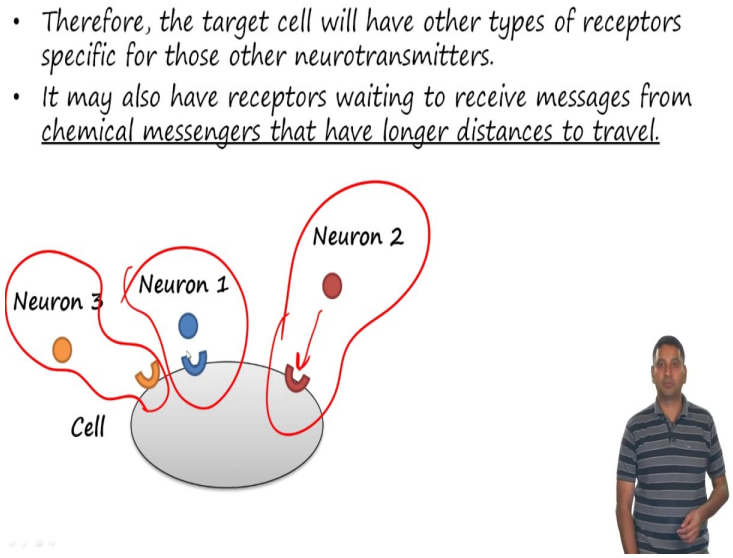

So the target cell will have other receptors for other neurotransmitters for example here you have this blue one which is interacting with neuron 1 and you may also have a red one which is interacting with neuron 2 and this the third one interacts with neuron 3 ok. Now but they may be longer distances that the signal has to travel for the same to interact with the receptor ok. So here for example a neuron 2, the distance that is travelled is much longer when compare to neuron 1 ok.

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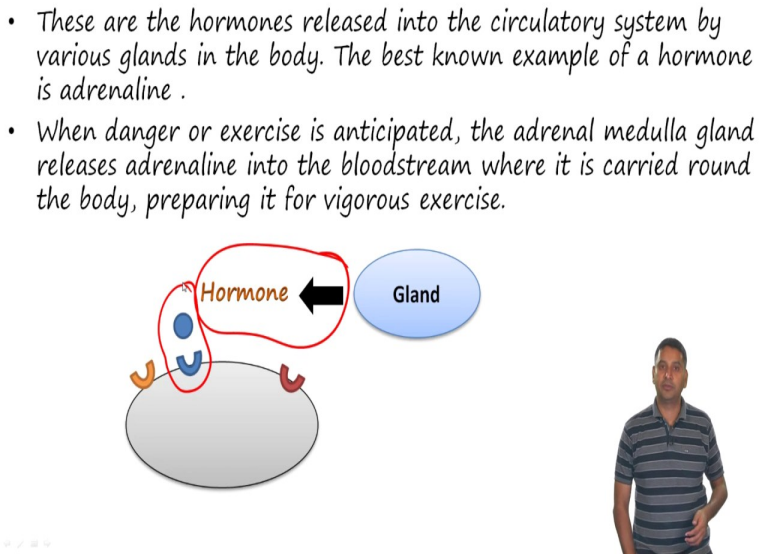

Now there are hormones which are also released into the circulatory system by glands, the example at which we looked at was adrenal gland which releases adrenaline ok. So this is a signal adrenaline is a signal when danger is anticipated ok so there is this fright flight or fight kind of response that is given out ok. So when the adrenaline, adrenal medulla gland releases adrenaline what happens is the body is preparing itself for vigorous exercise.

So a gland can release this hormone which then can go and interact with its receptor site ok.

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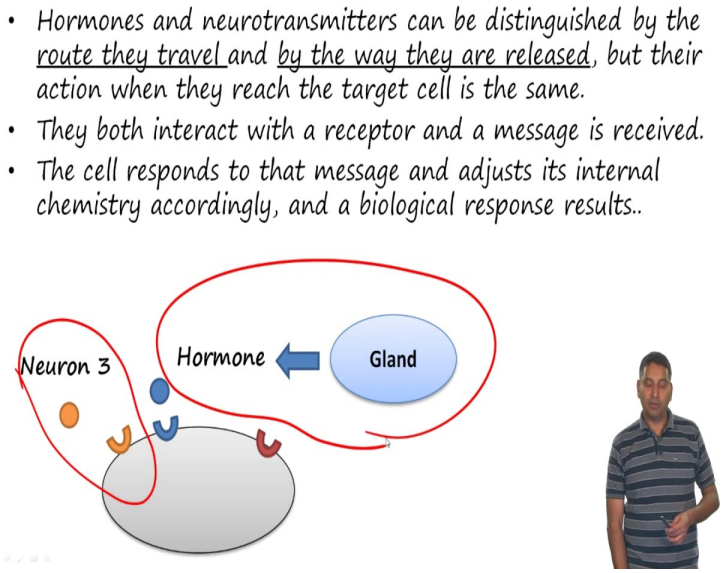

So hormones and neurotransmitters can be distinguished by the route they travel. So in the case of a neurotransmitters the neuron which is here communicates with the target which is fairly closed to it, whereas a hormone can be released into the blood stream and once the hormone gets into the blood stream it can interact with its target in various locations ok. The receptor on the cell interacts with both neurotransmitters and hormones can interact with a receptor and once the message is received the cell responds and the internal chemistry adjust itself so that a biological response is happens.

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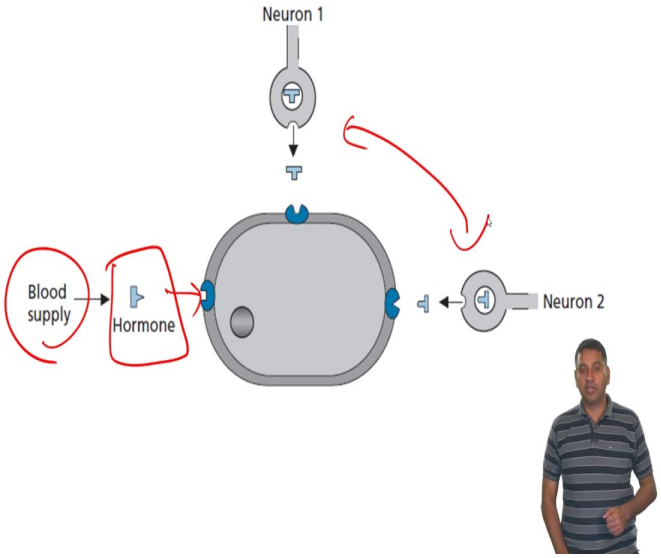

Ok, so in this schematic you see that the blood supply from through the blood supply a hormone can be produced or into the blood supply a hormone can be released and this hormone can interact with this receptor and offcourse you can have couple of neurons interacting with the target to give you a desired response.

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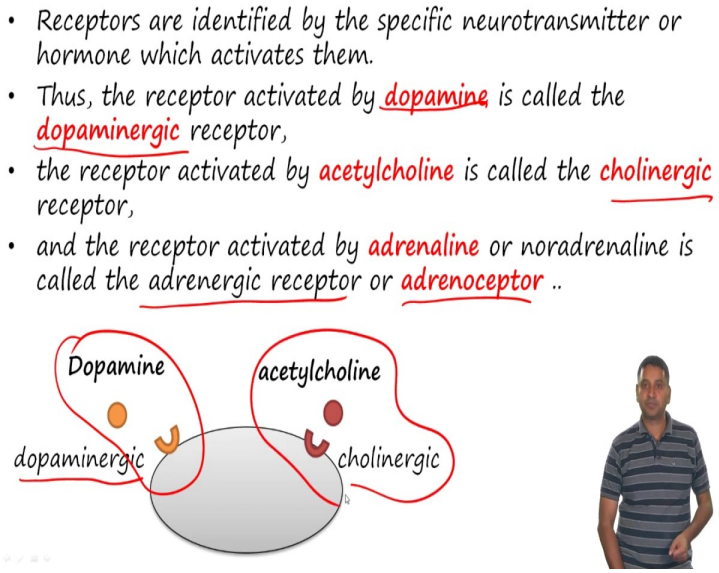

Receptors are typically identified by the specific neurotransmitter or hormone that interacts with them ok. So for example dopaminergic receptor is activated by dopamine and cholinergic receptors are activated by acetylcholine. You also have hormones which are for example

adrenaline which interact with adrenoceptor or adrenergic receptors ok. So in the schematic below you see that dopaminergic receptor interacts specifically with dopamine and acetylcholine interacts specifically with cholinergic receptors ok.

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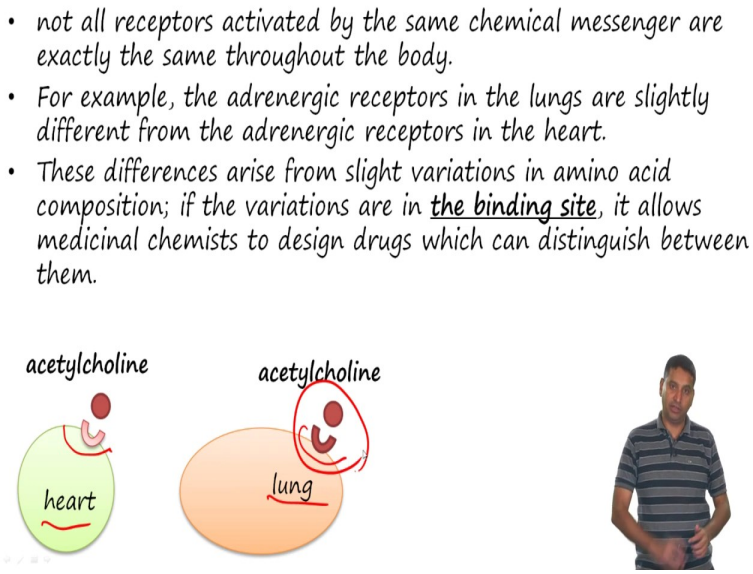

Now not all receptors are activated by the same chemical messenger in exactly the same way throughout the body. So the example that we can look at here is between a heart and the lung which has the same receptor but they can be structurally slightly different and the bindings site is perhaps a little bit different and so what happens is that even though the same small molecule in this case acetylcholine interacts with the receptor and the heart the different there could be different responses in the heart as well as in the lung ok.

Now these differences can be exploited to achieve what is known as selectivity. Let's say we want to selectively target the lung receptor over the heart receptor then one could make structural variations in the molecule that we want so that its specifically hits the lung and does not hit the heart.

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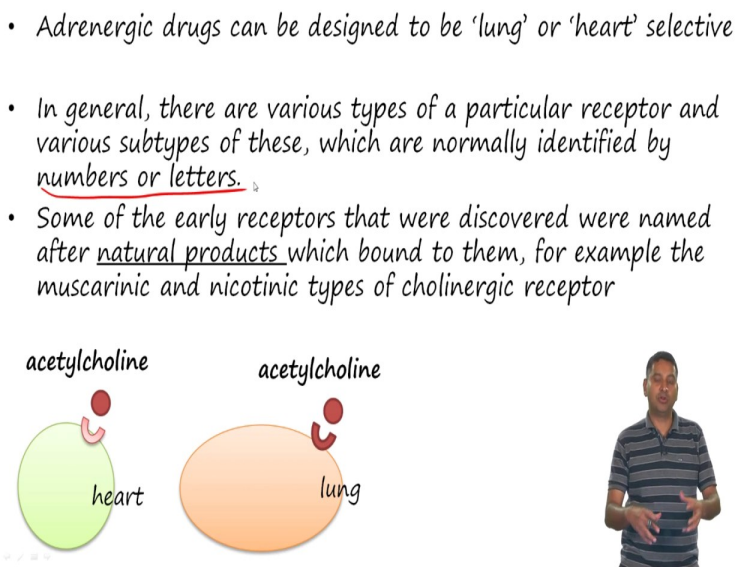

Now in general it is true that there are various types of a particular receptor just like we saw heart and lung can be different and these are normally identified by numbers or letters ok. Earlier many of the receptors that were discovered were named after natural products. So for example muscarinic receptor or nicotinic receptors are the ones that are subset of cholinergic receptors with this responds to muscarine or nicotinic ok.

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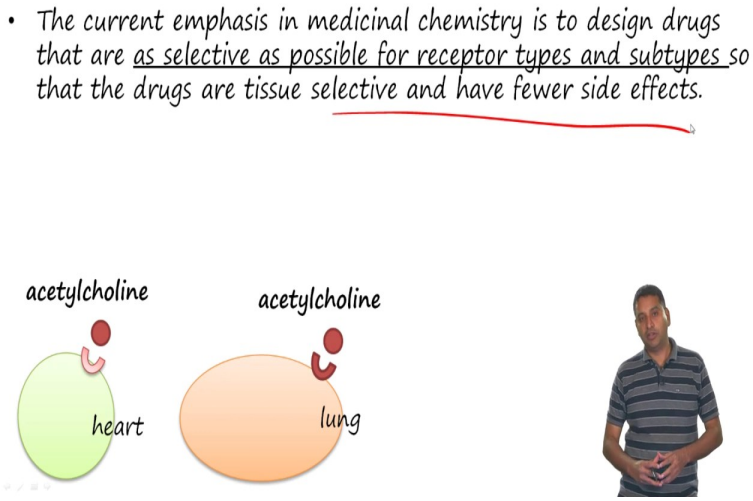

Now as I mentioned earlier the current emphasis is to design and developed selective receptors in binding compounds ok and not just receptors types but they also the sub type has to be appropriate. What this will result in is much fewer side effects if you can achieve selectivity.

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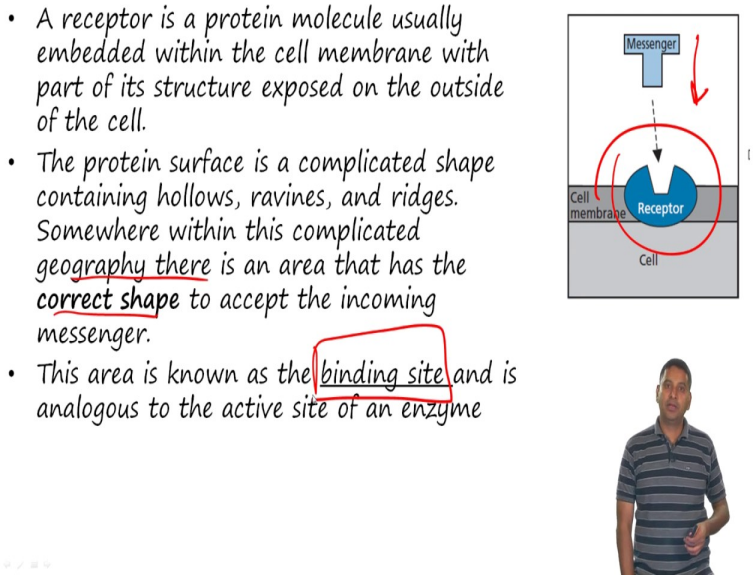

So a receptor is a protein which is usually located or embedded within the cell membrane. Now since this is located in the cell membrane it can interact with molecules which are outside the cell ok. The surface of the protein of is quite complicated and it can have hollows, ravines and ridges and which can which form the right shape for the messenger to come and bind. Broadly speaking

in this area where the receptor or where the messenger binds is known as a binding site. The analogy that we have learned before is the active site of an enzyme.

So the binding site of receptor is very similar to the active site of an enzyme.

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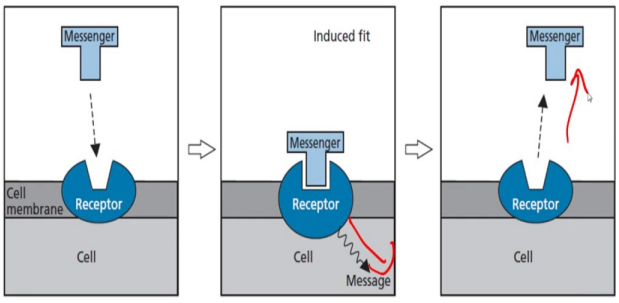

When the chemical messenger fits into this site it 'switches on' the receptor molecule and a message is received

Now after the messenger binds, what happens is that there is a sort of a induced fit that occurs and this switches on the receptor and the message is transmitted. Once the message is transmitted and the job is done then the messenger can be released back into the released out from the receptor.

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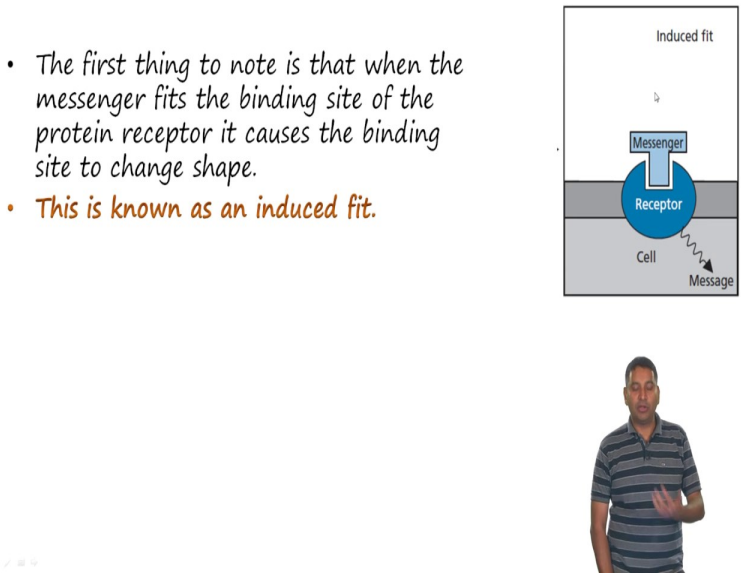

Offcourse the first thing that we need to note is that the messenger fits the binding site of a protein receptor perfectly ok and this fit what we call as an induced fit. So induced fit is nothing but when you have the receptors sort of changing its shape as we saw in our enzyme active site to a little bit to bind the messenger.

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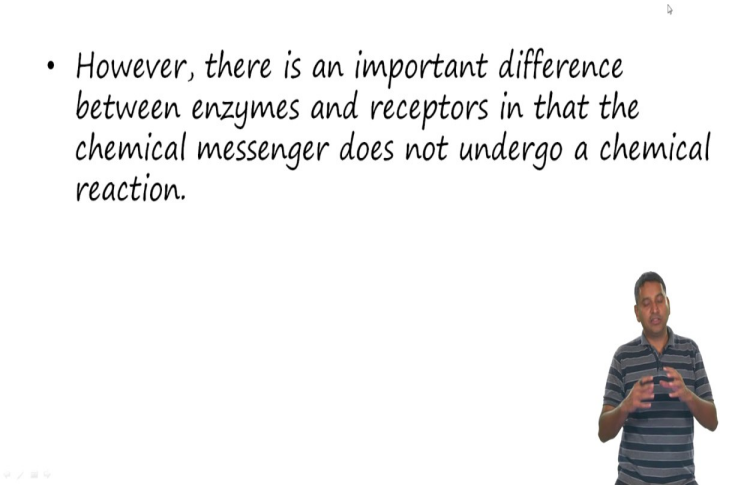

The important difference between enzymes and receptors is that the chemical messenger that transmits the signal in the case of receptor remains unchanged whereas in an enzyme the

substrate binds to the protein undergoes a chemical reaction and is transformed to another product. So that is a very important difference between enzymes and receptors.

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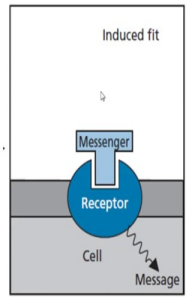
- It fits into the binding site of the receptor protein, passes on its message, and then leaves unchanged.
- If no reaction takes place, what has happened?
- How does the chemical messenger tell the receptor its message and how is this message conveyed to the cell?



Now when it passes once its fits into the binding site of the receptor and passes on the message and if it is unchanged then what exactly is happening? Question is how does the chemical messenger tell the receptor its message and how is this message convey to the cell?

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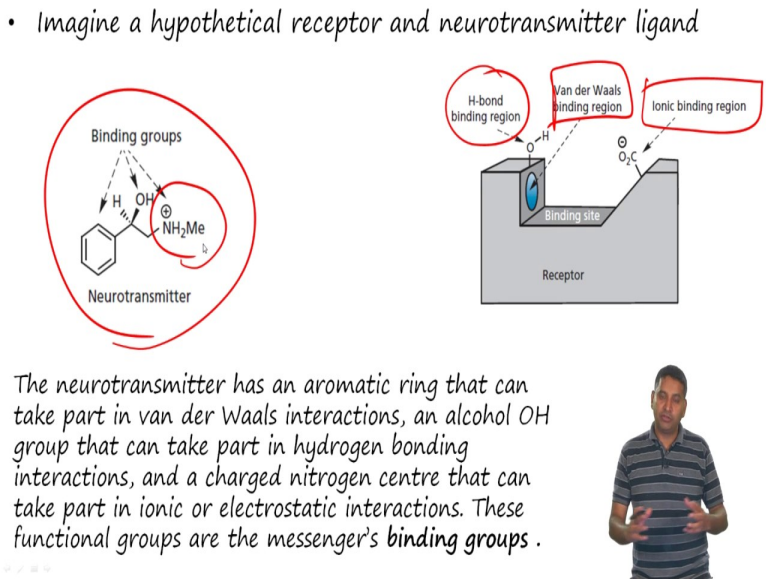

In order to understand this let us imagine a hypothetical receptor which has a hydrogen bonding region, a Vander Walls binding region and a ionic binding region. So the hydrogen bonding is given by a hydroxyl group and perhaps there is a region small aromatic residue which can result in Vander Walls binding and there could be a free carboxylate ion which does ionic binding. Now let's imagine the ligand which binds to this receptor as the structure shown here.

So this structure has a aromatic ring which can do Vander Walls binding, it also has a free hydroxyl group which can perhaps do hydrogen bonding to the hydroxyl group in the receptor's surface and it also has a ammonium salt which can bind to the carboxylate ion ok. So it appears that the neurotransmitter and the receptor are very well placed to bind to each other.

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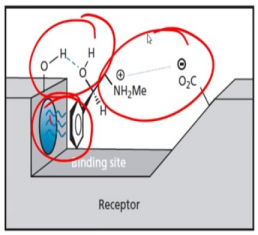
- Binding site contains three binding regions which contain functional groups that are complimentary to the binding groups of the messenger.
- The messenger fits into the binding site such that intermolecular interactions take place between the messenger's binding groups and the receptor's binding regions
- However, the fit is not perfect. In the diagram, there are good van der Waals and hydrogen bond interactions, but the ionic interaction is not as strong as it could be...



Now after it binds imagine that it binds and if this interaction occurs the Vander Walls interaction occurs and the hydrogen bonding interaction occurs and these are extremely complimentary and therefore one would imagine that this would be a fairly good binding effect. But if you notice here the ammonium salt is interacting with the carboxylate but it appears that the fit is not perfect ok. So therefore the ionic interaction is not as strong as it could be.

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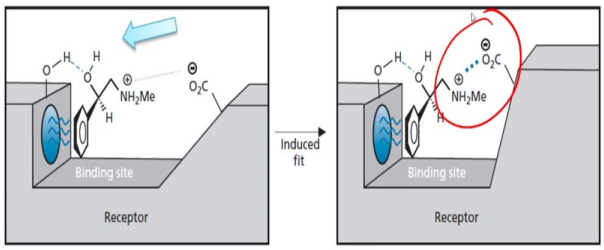

- The ionic binding region is close enough to have a weak interaction with the messenger, but not close enough for the optimum interaction.
- The receptor protein therefore alters shape to bring the carboxylate group closer to the positively charged nitrogen and to obtain a stronger interaction.

But if the receptor changes its conformation a bit if it gets closer to the ammonium salt then it is possible that this binding interaction becomes stronger and that maybe the right or optimum interaction which results in a strong binding ok. So this model that we have looked at it is a hypothetical model but it help is understand the concept of an induced fit. So, there are couple of interactions which are already quite strong but maybe there are few other interactions that will happen if the protein can undergo a conformation change and together once this conformation change occurs or a series of conformation change occur then a strong interaction results.

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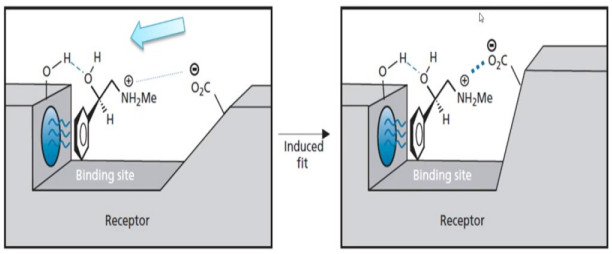

- The shape of the binding site is altered and an induced fit has taken place.

In reality, both the messenger and the binding site take up different conformations or shapes to maximize the bonding forces between them.

Ok, so this is called as an induced fit, in reality both the messenger and the binding site would probably undergo conformational changes to maximize the bonding forces between them