Medicinal Chemistry
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Cholinergics

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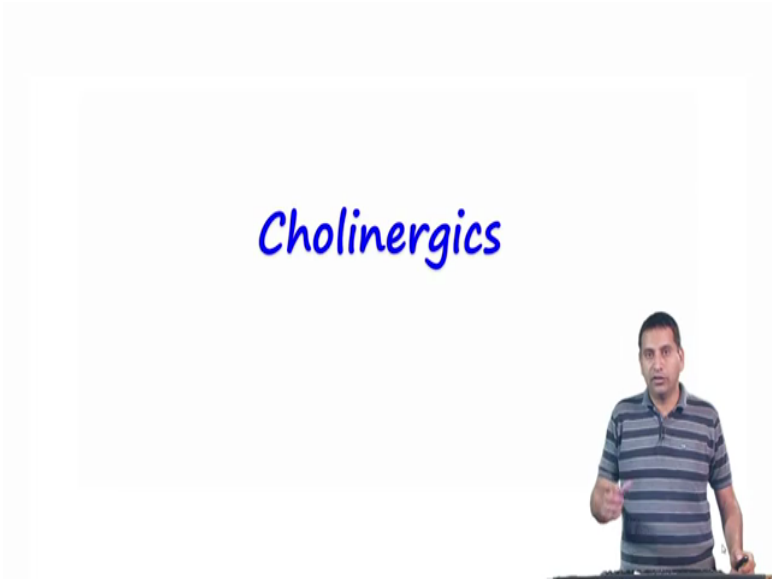

Ok, so in today is lecture we will look at various aspect of the choline based signalling system, acetylcholine basing link system and what we will look at is the compounds that can act as ligands for these receptors as well as antagonists for these receptors and there is a process of hydrolysis of the acetylcholine and so therefore this ester hydrolysis is also important.

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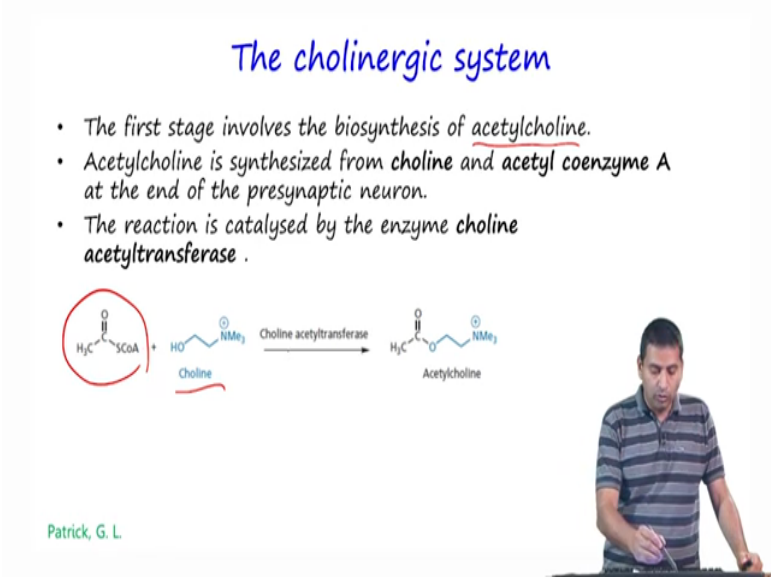

So let us look at the cholinergic system, the first (sys) stage of the system involves the biosynthesis of acetylcholine ok, acetylcholine is synthesized from choline and acetyl coenzyme, so here is choline and here is acetyl coenzyme which we will again looked at previously and the end of the presynaptic neuron, so this reaction is catalysed by an enzyme known as choline acetyltransferase.

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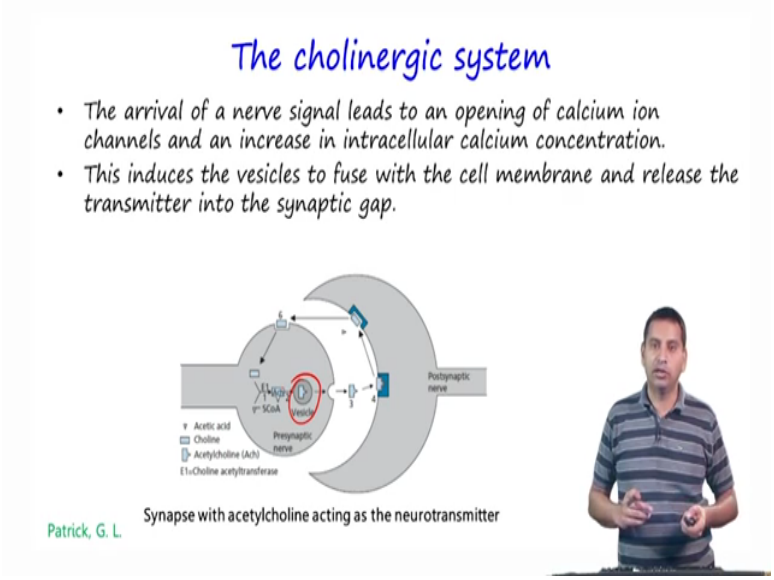

So the arrival of a nerve signal leads to an opening of calcium ion channels and leads to an intracellular increase in calcium concentration, this induces the vesicles to fuse with the cell membrane and release the transmitter at the synaptic gap, so here is an illustration of the

synaptic gap and what we have already discussed previously in detail is that there is actually a gap between the synapse in which is where the chemical signals are actually going to play a major role.

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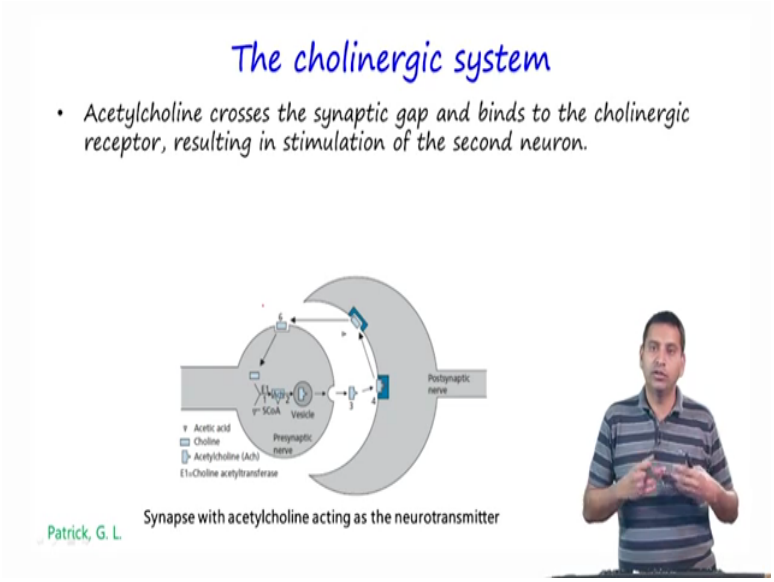

So acetylcholine actually crosses the synaptic gap and binds to the cholinergic receptor these results in the stimulation of the second neuron.

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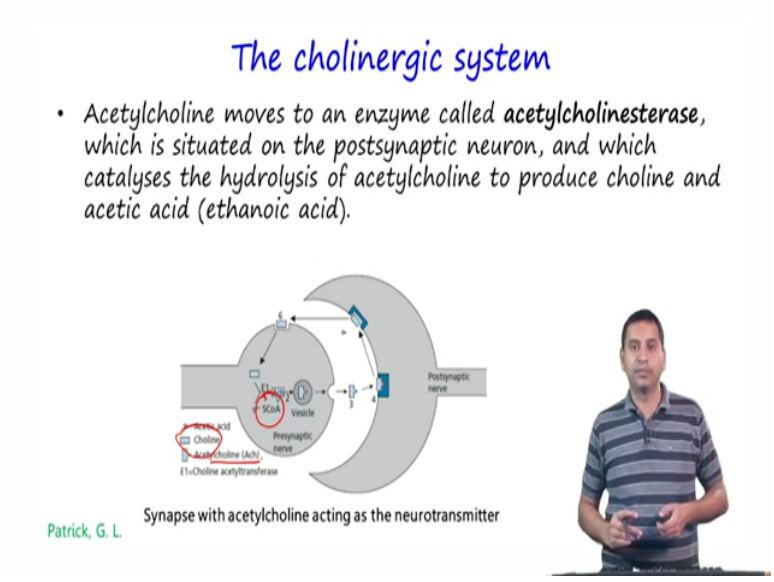

So acetylcholine moves to an enzyme called as acetylcholineesterase which is situated on the postsynaptic neuron and then these catalyses the hydrolysis of acetylcholine to produce choline and acetic acid. So here is the enzyme which then produces choline and acetic acid.

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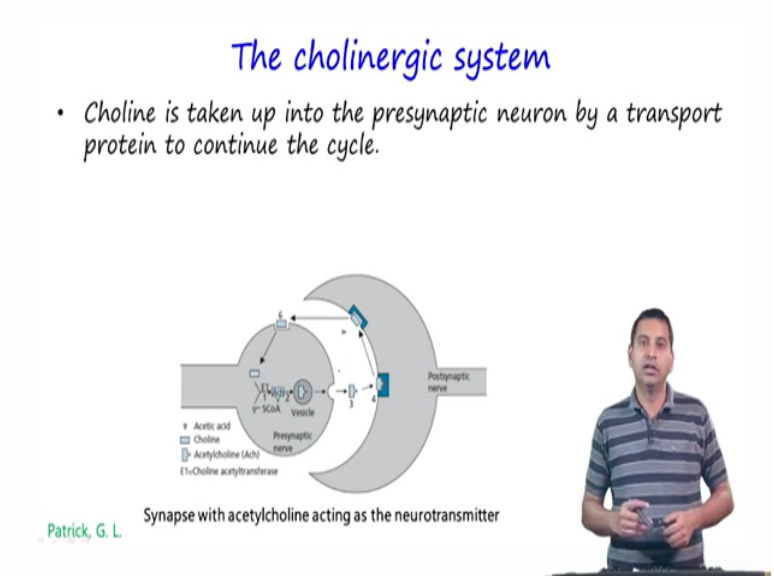

The choline is then taken up by the presynaptic neuron by transport protein to continue the cycle.

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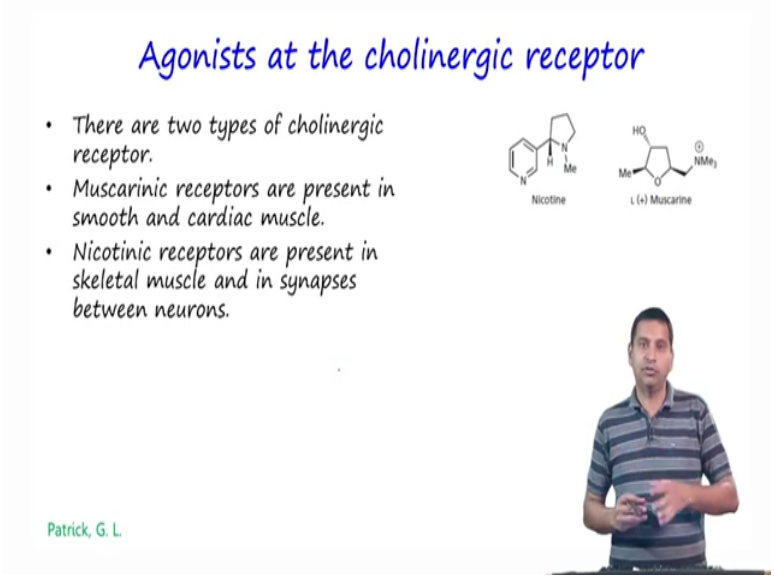

So there are two types of cholinergic receptors, so one is the Muscarinic receptor which is present in smooth and cardiac muscle and the other one is the Nicotinic receptor which is present in skeletal muscle and in synapses between neurons.

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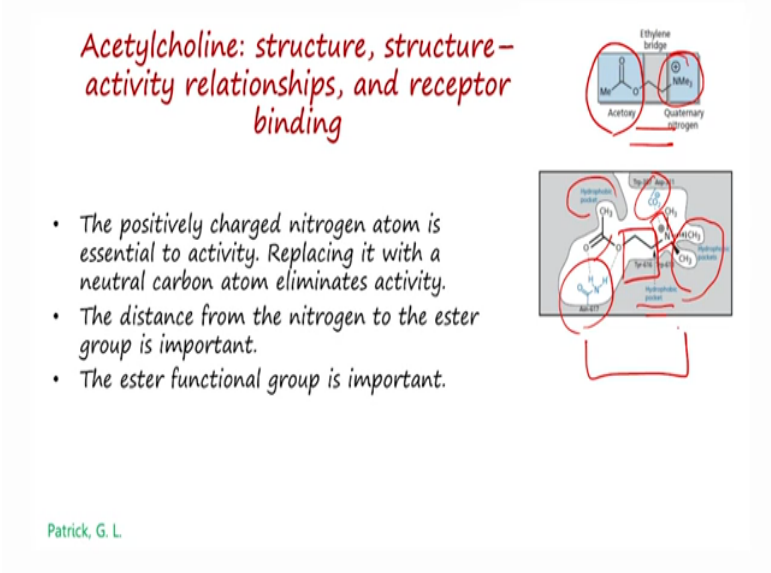

So what we could do is we need to develop agonists so that we can enable or improve neural transmission. So in order to understand this let us look at some of the structure activity relationships and receptor binding of this molecule. So here is the structure of acetylcholine so there is a quaternary nitrogen over here and then there is an ethylene bridge followed by an acetoxy group, ok and here below is the way in which this binds there is a hydrophobic pocket to which the acetyl group binds and then there is a hydrophobic pocket to which these methyl groups bind and there is an aspartate which then interacts through ionic bonding to the positively charged nitrogen and then there is another hydrophobic pocket which then binds to this bridge, ok and lastly this acetyl group also interacts with a (())(03:32) 617.

So this type of interaction are very important, so what has been shown is that the positively charged nitrogen is absolutely essential for activity. So now if you replace this nitrogen with a neutral carbon eliminates activity also the distance from the nitrogen to the ester is also important. The ester functional group itself is really important.

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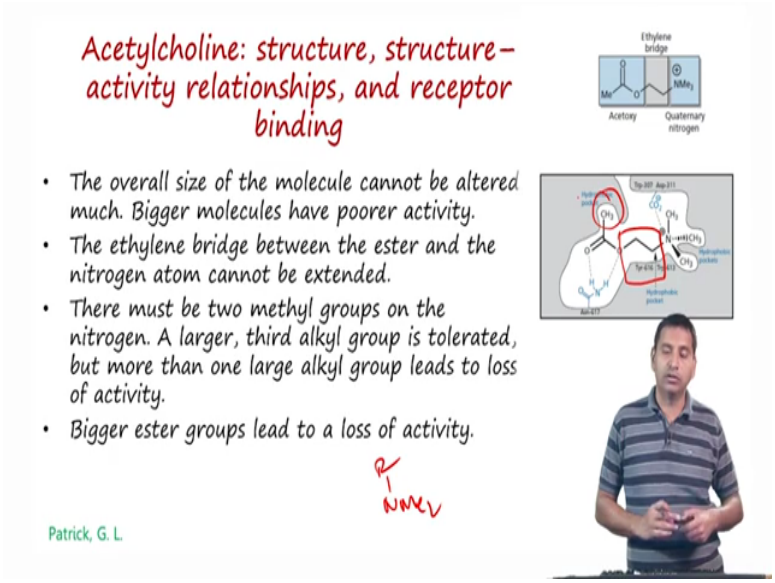

And importantly the overall size of the molecule cannot be altered much, so bigger molecules have actually poorer activity. So the ethylene bridge which is present between this cannot be extended further because then again sort of reduces the interaction so it is quite optimal and there must be two methyl groups on the nitrogen, so a larger third alkyl group is tolerated but more than one large alkyl group leads to loss of activity, so we are restricted to nme to R.

Now on the other side if you have larger esters, so for example if you have larger esters then acetyl group then that also results in loss of activity, so we are fairly restricted in what we can do for SAR.

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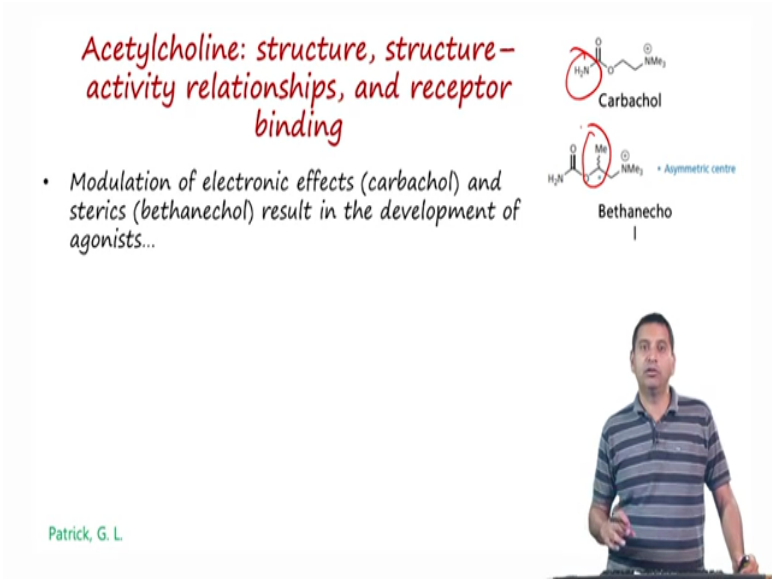

So one method that has been used is to modulate the electronic effects in the case of carbachol, so what is done here is to replace the ester with a carbon made and that helps in (modif) modifying the electronic effects. The other way is to actually modify sterics so here what we have done is to put a methyl group and it also of course creates an asymmetric center and these help in the development of agonists.