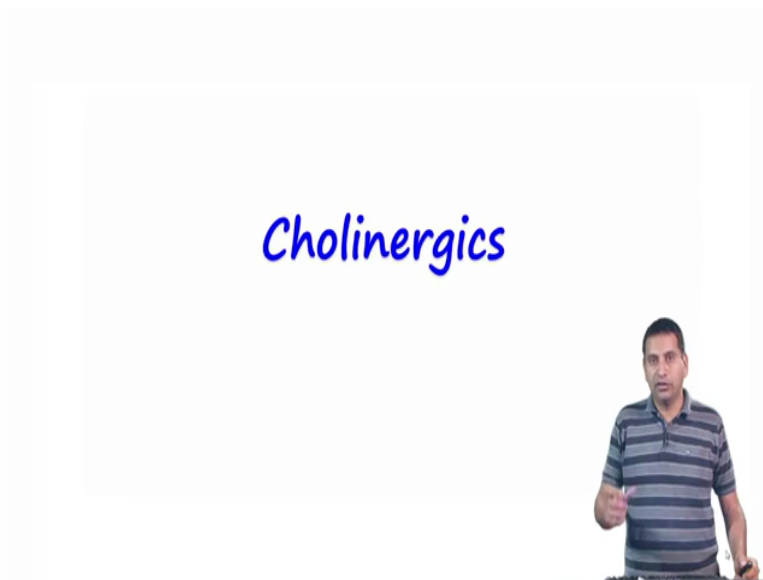


Medicinal Chemistry
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Indian Institute of Science Education and Research, Pune
Cholinergics

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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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The cholinergic system

- The first stage involves the biosynthesis of acetylcholine.
- Acetylcholine is synthesized from choline and acetyl coenzyme A at the end of the presynaptic neuron.
- The reaction is catalysed by the enzyme choline acetyltransferase.

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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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The cholinergic system

- The arrival of a nerve signal leads to an opening of calcium ion channels and an increase in intracellular calcium concentration.
- This induces the vesicles to fuse with the cell membrane and release the transmitter into the synaptic gap.

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Synapse with acetylcholine acting as the neurotransmitter

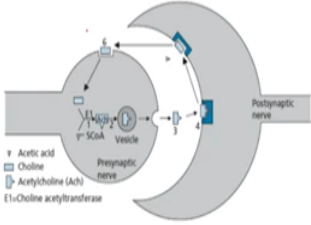
So the arrival of a nerve signal leads to an opening of calcium ion channels and leads to an intracellular increase in calcium concentration, this induces the vesicles to fuse with the cell membrane and release the transmitter at the synaptic gap, so here is an illustration of the

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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The cholinergic system

- Acetylcholine crosses the synaptic gap and binds to the cholinergic receptor, resulting in stimulation of the second neuron.



Patrick, G. L. Synapse with acetylcholine acting as the neurotransmitter

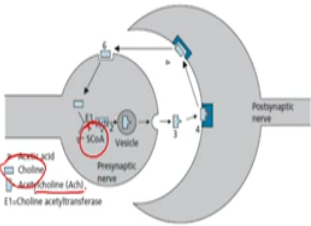
The diagram illustrates the synthesis of acetylcholine (ACh) in a presynaptic neuron. Acetic acid and choline combine, catalyzed by the enzyme E1-Choline acetyltransferase, to form ACh. ACh is then packaged into vesicles. Upon an action potential, vesicles fuse with the presynaptic membrane, releasing ACh into the synaptic gap. ACh binds to receptors on the postsynaptic neuron, leading to its stimulation. A legend identifies the components: Acetic acid (green triangle), Choline (blue square), Acetylcholine (ACh) (red circle), and E1-Choline acetyltransferase (yellow rectangle).

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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The cholinergic system

- Acetylcholine moves to an enzyme called *acetylcholinesterase*, which is situated on the postsynaptic neuron, and which catalyses the hydrolysis of acetylcholine to produce choline and acetic acid (ethanoic acid).



Patrick, G. L. Synapse with acetylcholine acting as the neurotransmitter

This diagram is identical to the previous one but highlights the breakdown of ACh. ACh is shown moving from the synaptic gap to the postsynaptic neuron, where it is hydrolyzed by the enzyme acetylcholinesterase. The products are choline and acetic acid. Red circles and arrows in the diagram emphasize the ACh and the enzyme acetylcholinesterase.

So acetylcholine moves to an enzyme called as acetylcholinesterase 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 cholinergic system

- Choline is taken up into the presynaptic neuron by a transport protein to continue the cycle.

The diagram illustrates the cycle of acetylcholine (ACh) at a synapse. Inside the presynaptic neuron, Acetyl-CoA and Choline combine to form ACh, a reaction catalyzed by the enzyme Choline acetyltransferase. ACh is then packaged into vesicles. Upon stimulation, these vesicles fuse with the presynaptic membrane, releasing ACh into the synaptic cleft. ACh binds to receptors on the postsynaptic nerve. After release, ACh is broken down into Acetic acid and Choline. Choline is then transported back into the presynaptic neuron by a transport protein to be reused for ACh synthesis.

Patrick, G. L. Synapse with acetylcholine acting as the neurotransmitter

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

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Agonists at the cholinergic receptor

- There are two types of cholinergic receptor.
- Muscarinic receptors are present in smooth and cardiac muscle.
- Nicotinic receptors are present in skeletal muscle and in synapses between neurons.

The image shows the chemical structures of two cholinergic agonists. Nicotine is a pyridine ring with a methylated pyrrolidine ring attached. L (+) Muscarine is a five-membered furanose ring with a methyl group at the 2-position, a hydroxyl group at the 3-position, and a trimethylammonium group at the 4-position.

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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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Acetylcholine: structure, structure-activity relationships, and receptor binding

- The positively charged nitrogen atom is essential to activity. Replacing it with a neutral carbon atom eliminates activity.
- The distance from the nitrogen to the ester group is important.
- The ester functional group is important.

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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 (O)(03:32) 617.


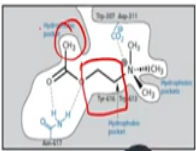
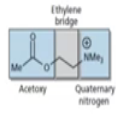
So this type of interaction are very important, so what has been shown is that the positively charged nitrogen is absolutely essential for activity. So now if you replace this nitrogen with a neutral carbon eliminates activity also the distance from the nitrogen to the ester is also important. The ester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

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Acetylcholine: structure, structure-activity relationships, and receptor binding

- The overall size of the molecule cannot be altered much. Bigger molecules have poorer activity.
- The ethylene bridge between the ester and the nitrogen atom cannot be extended.
- There must be two methyl groups on the nitrogen. A larger, third alkyl group is tolerated, but more than one large alkyl group leads to loss of activity.
- Bigger ester groups lead to a loss of activity.

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R
NMe₂

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.

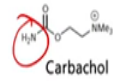
Now on the other side if you have larger esters, so for example if you have larger esters then acetyl group then that also results in loss of activity, so we are fairly restricted in what we can do for SAR.

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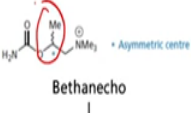
Acetylcholine: structure, structure-activity relationships, and receptor binding

- Modulation of electronic effects (carbachol) and sterics (bethanechol) result in the development of agonists...


Patrick, G. L.



Carbachol



Bethanecho
|



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.