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The Direct Cholinomimetics and Cholinergic Blocking Agents Depend on Stereo Specificity of Cholinergic Receptors

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Abstract

The cholinergic receptors are the site of action of acetylcholine (Ach) and acetylcholine like substance and anti-cholinergic agents, these receptors either muscarinic receptors or nicotinic receptors the exactly difference between them the area of receptor, where the muscarinic receptor is short than nicotinic receptor (nearly 4.5 and 6 Angstrom, respectively) and the muscarine act on muscarinic receptors and nicotine act on nicotinic receptors. The direct cholinomimetics and cholinergic blocking agents are characterized by chemical features adjustment with these receptors. This can be explained by the structure activity relationship (SAR) of direct cholinomimetic and cholinergic blocking agent drugs. The important examples of stereo specificity of receptors are hexamethonium and decamethonium, which is binding with the nicotinic receptor by specific mechanism (via width and length respectively of the receptor).

Keywords: stereo specificity, cholinergic receptors, direct cholinomimetics, targeting, anti-muscarinic, M1, M2 and nicotinic receptors, Acetylcholine, cholinergic activity, anti-cholinergic activity

1. Introduction

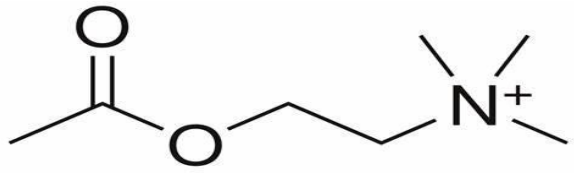
The direct cholinomimetics are necessary to similar acetylcholine which is the key of action of the receptor, i.e., the direct cholinomimetics must be contain quaternary nitrogen, ethylene spacer and acetyloxy groups, the quaternary nitrogen must be substituted with tri-methyl in case of agonist or with tri-ethyl in case of antagonist, in agonist state the nitrogen must be quaternary but in case of antagonist may be tertiary nitrogen. The ethylene spacer may be

substituted one hydrogen of them by methyl, if the alpha-carbon substituted the resulted compound is nicotinic more than muscarinic but if the beta-substituted the resulted compound is muscarinic more than nicotinic, also when substitute the acetyloxy group by amide group the activity will present and has long duration.

From the previous introduction we will resulting the direct cholinomimetics and cholinergic blocking agents must have at least six atoms start by nitrogen, two carbon spacer, ester group (two distant atoms oxygen and carbonyl) and lastly methyl group (alkyl group).

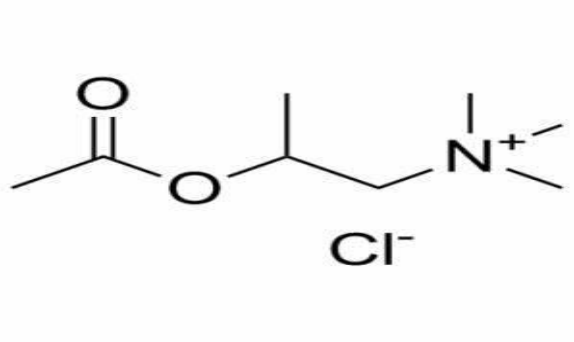
2. Chemistry and Cholinergic Actions

Direct cholinomimetics firstly ***Ach*** is the key of action of cholinergic receptor.



The Ach is a power full parasympathetic nerve stimulation, it is biosynthesized in the body from the serin amino acid decarboxylated which react with choline and acetyl group from acetyl-coA (Ach). The major side effect of Ach its degraded by acetylcholinesterase, so it is rarely clinically used in medicine.

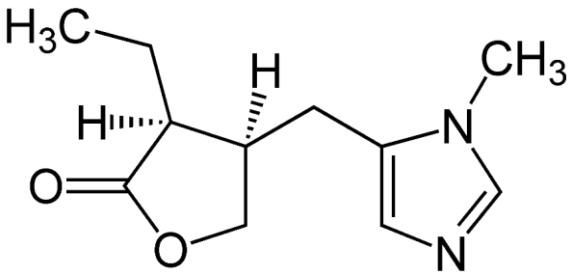
Methacholine



Methacholine is similar to Ach but differ in one hydrogen of beta-carbon replaced by methyl group which act on muscarinic receptor more than nicotinic receptor (comparing with the alpha-hydrogen replaced which give nicotinic more than muscarinic), where it used muscarinic action to reduce secretion of GIT…etc. The methacholine has optical activity due to chiral carbon.

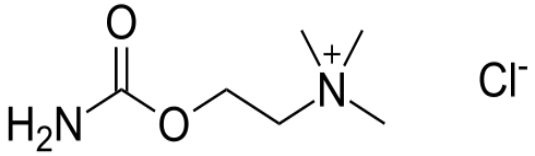
N.B. S(+) enantiomer is equal in action on muscarinic and nicotinic receptor, while R(-) enantiomer is 20-times less potent, methacholine the first synthetic direct cholinomimetic drug.

Pilocarpine



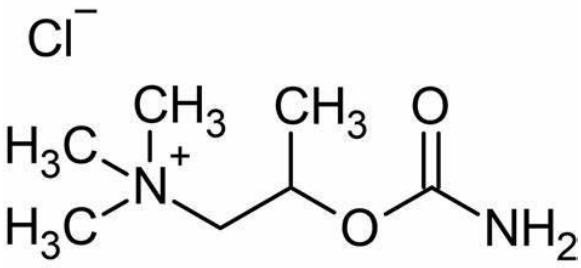
Pilocarpine is a natural alkaloid muscarinic agonist which cause miosis of eye so used in treatment of glaucoma as sterile isotonic eye drops.

Carbachol



It is the mirror image of Ach but replace the methyl group with amino group, the carbachol characterized by long duration of action due to carbamate which give the compound steric and electronic effects that responsible for its long duration and delayed of its degradation by Ach esterase.

Bethanechol

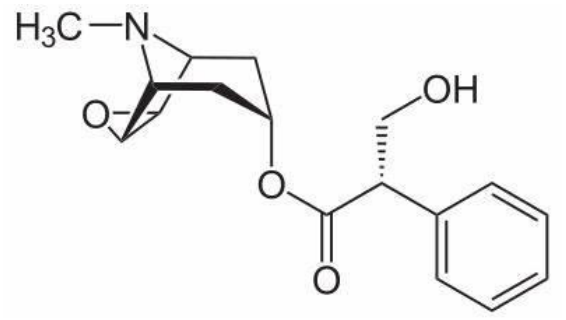


It is analogue of methacholine, where the methyl group of esters replaced by amino group which also has a long duration due to carbamate group which also give steric and electronic effects as a muscarinic agonist.

Atropine

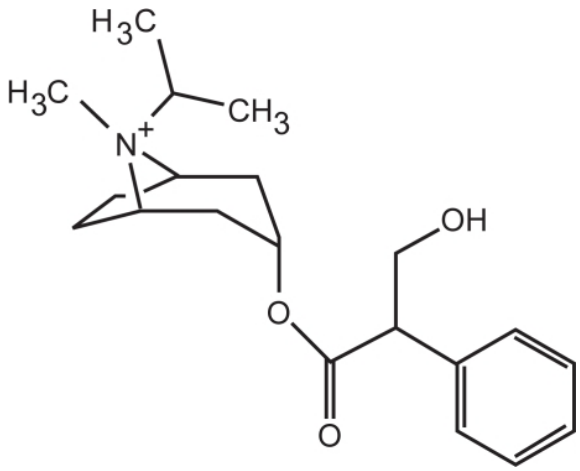
Atropine is analogue for hyoscyamine, the prototype of cholinergic blocking agent which act on muscarinic receptor and give the opposite action of direct cholinomimetics e.g., dry mouth, mydriasis, flushing… etc. notice that the role of features of chemical structure which act on cholinergic receptor either agonist or antagonist, the most important feature the six atoms stated by nitrogen, two carbons, ester group, and alkyl group.

Scopolamine (Hyoscine)



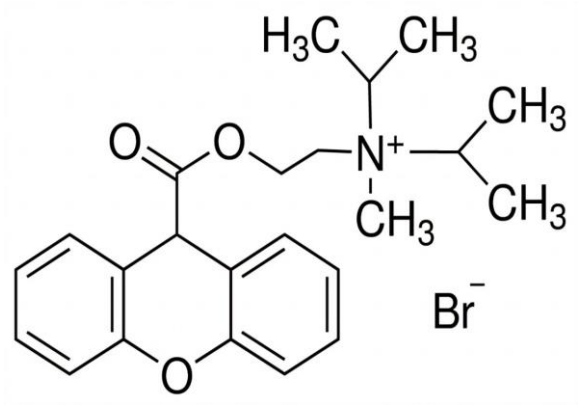
The natural alkaloid scopolamine is a mirror image of hyoscine which are cholinergic blocking agent acting on muscarinic receptor.

Ipratropium



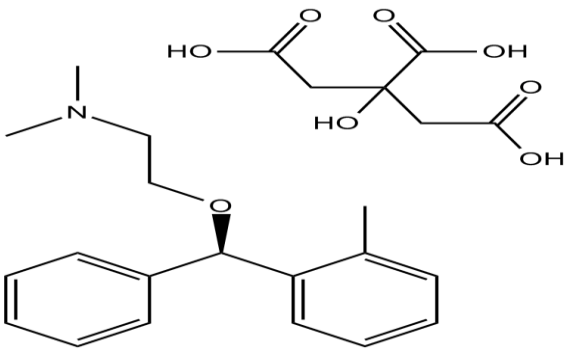
Anti-muscarinic bronchodilator synthetic agent from atropine by replaced of hydrogen on nitrogen by isopropyl.

Propantheline



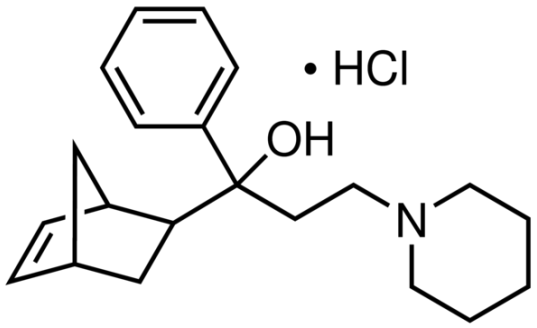
Propantheline is anti-cholinergic (muscarinic antagonist) anti-spasmodic drug.

Orphenadrine Citrate



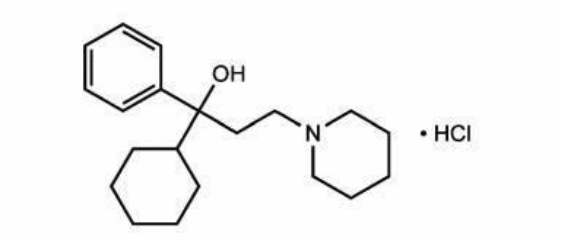
Anti-cholinergic (muscarinic antagonist), Anti-histaminic like diphenhydramine, Central muscle relaxant and anti-parkinsonian drug (symptomatic treatment).

Biperidine



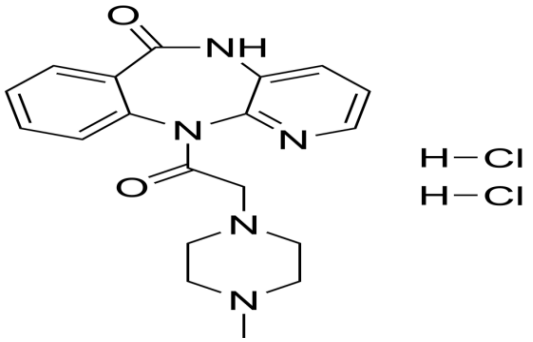
Anti-cholinergic (muscarinic antagonist) anti-parkinsonian drug.

Trihexyphenidyl Chloride



Anti-cholinergic anti spasmodic, anti parkinsonism drug.

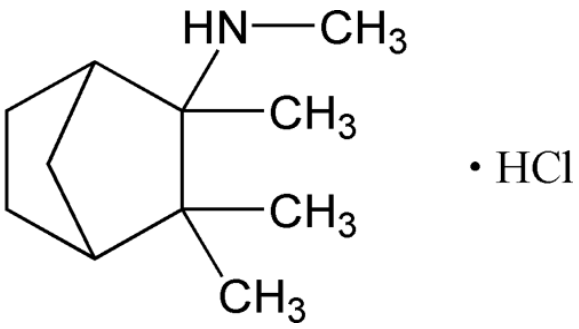
Pirenzepine



The only M1 antagonist (selective muscarinic 1 blocker used in treatment of peptic ulcer anticholinergic drug)

N.B. All the above-mentioned drugs are non-specific muscarinic antagonist M1 and M2.

Nicotinic-Blockers Ganglionic Blocker (N1-Blocker) Mecamylamine Hydrochloride



Anti-cholinergic nicotinic blocker (N1-ganglionic blocker) used in treatment of hypertension with caution due to cause sever hypotension, whereas the all ganglia are blocked (either sympathetic and parasympathetic).

Neuromuscular blocking agents (N2-Blockers)

These is the compounds which act as anti-cholinergic and act on the motor end plate (nerve embedded directly in the muscle), and divided into non-depolarizing and depolarizing agents.

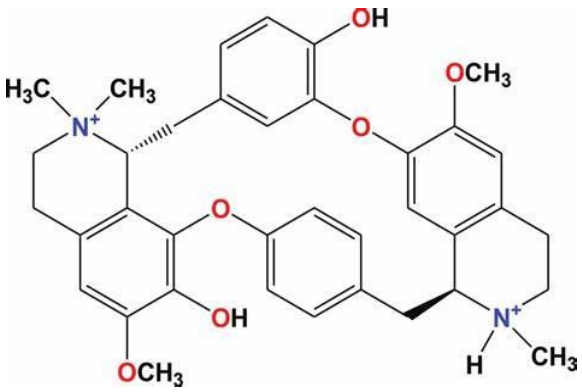
The difference between depolarizing blocking and non-depolarizing agents.

(The depolarizing firstly stimulates the receptor i.e., in small dose, and finally blocking the receptor e.g., nicotine).

Are the smokers exposed to parkinsonism more than non-smokers????

Non-Depolarizing

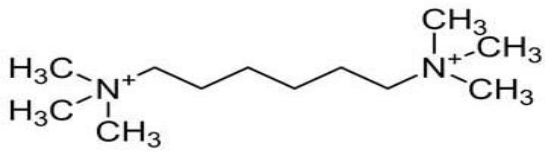
Agent D-Tubocurarine

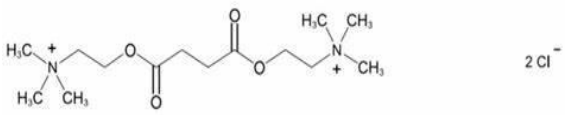


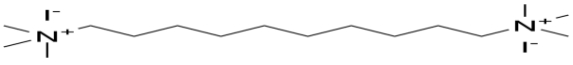
Anti-cholinergic (N2 antagonist) non-depolarizing blocking agent, this drug has some muscarinic blocker, but its essential action at the N2 receptor.

Depolarizing Blocking Agents

Hexamethonium, Decamethonium and Succinyl Choline







All of these drugs are neuro muscular blocking active, these compounds have structures contain eight atoms as hexamethonium and twelve atoms decamethonium and succinyl choline.

3. Conclusion

As we previously mentioned the Hexamethonium fit with receptor by width and the Decamethonium fit with N2 receptor by the length. The succinyl choline explains this conclusion where when it longed (expanded) it is like decamethonium i.e., fit with receptor by length and when bended it is like hexamethonium and fit with receptor by width.

All the mentioned explain stereospecificity of cholinergic receptors.

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