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College of Pharmacy
Dep. of Pharmaceutical Chemistry
Organic Pharmaceutical Chemistry II



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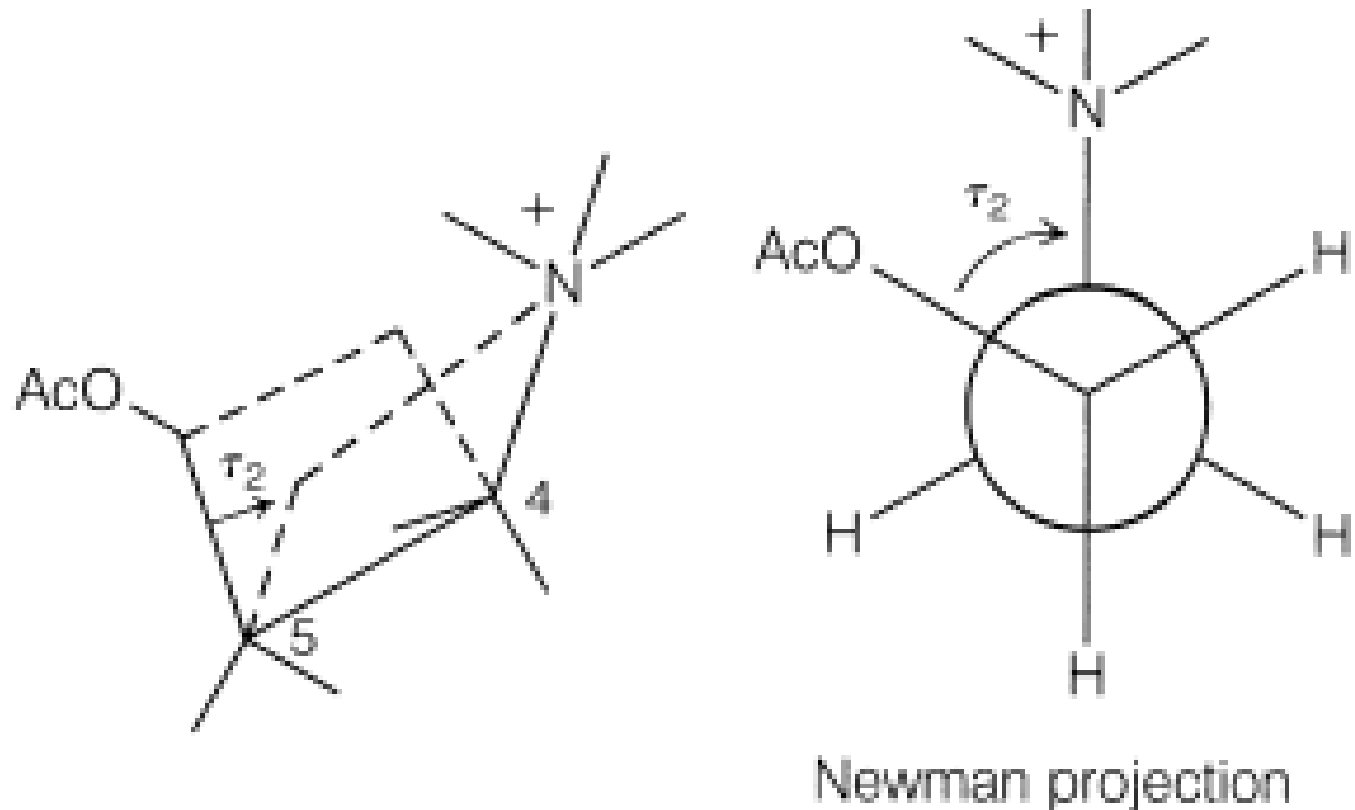
CHOLINERGIC AGONISTS

Cholinergic Stereochemistry

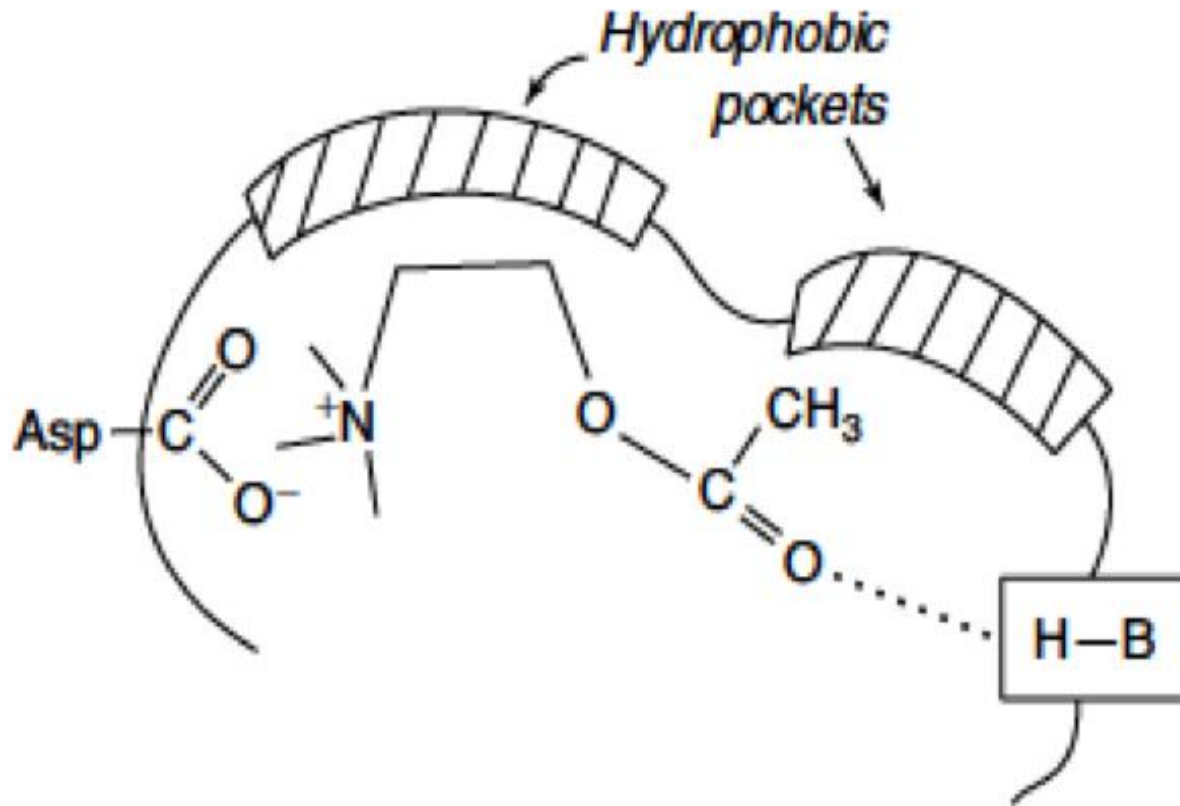
A torsion angle is defined as the angle formed between two planes, for example, by the O1-C5-C-4N atoms in ACh.

The torsion angle (O-C-C-N) determines the spatial orientation of the cationic head of ACh to the ester group.

ACh is transformed from the gauche conformation in the free state to a nearly trans conformation when bound to the nicotinic receptor.



Structure–Activity Relationships (SAR)



Hypothetical structure of the muscarinic receptor.

ACh

- The ACh contain three core groups:
- the *onium group*
- the *ester* function, and
- the *choline* moiety.

The onium group

- Is essential for intrinsic activity.
- Binds to the negatively charged aspartic acid residue in the third of the seven transmembrane helices of the muscarinic receptor.
- The trimethylammonium group is the optimal functional moiety for activity, although some significant exceptions are known (e.g., pilocarpine and nicotine).

The ester group

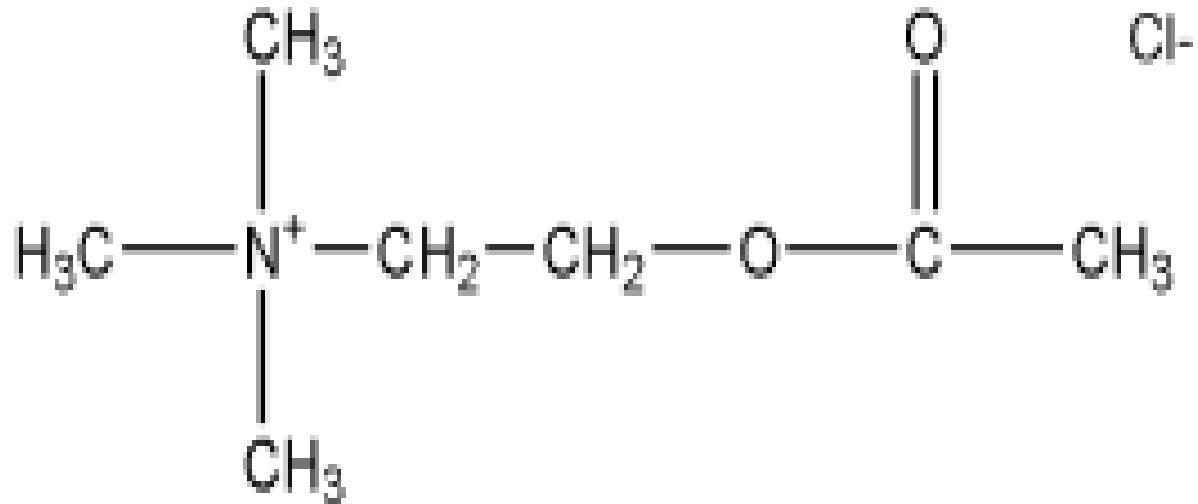
- Contributes to the binding of the compound to the muscarinic receptor
- Forms a hydrogen bond with threonine and asparagine residues.
- The presence of the acetyl group in ACh is not as critical as the size of the molecule, so that for maximal muscarinic activity, the onium group should be followed by a chain of five atoms; (*the five-atom rule*).
- Shortening or lengthening the chain of atoms that separates the ester group from the onium moiety reduces muscarinic activity.

The choline moiety

- An α substitution on *the choline moiety* decreases both nicotinic and muscarinic activity, although muscarinic activity is decreased to a greater extent.
- Nicotinic activity is decreased to a greater degree by substitution on the β carbon.
- Which one does exhibit more muscarinic than nicotinic activity, α -methylcholine or β -methylcholine ?

Products

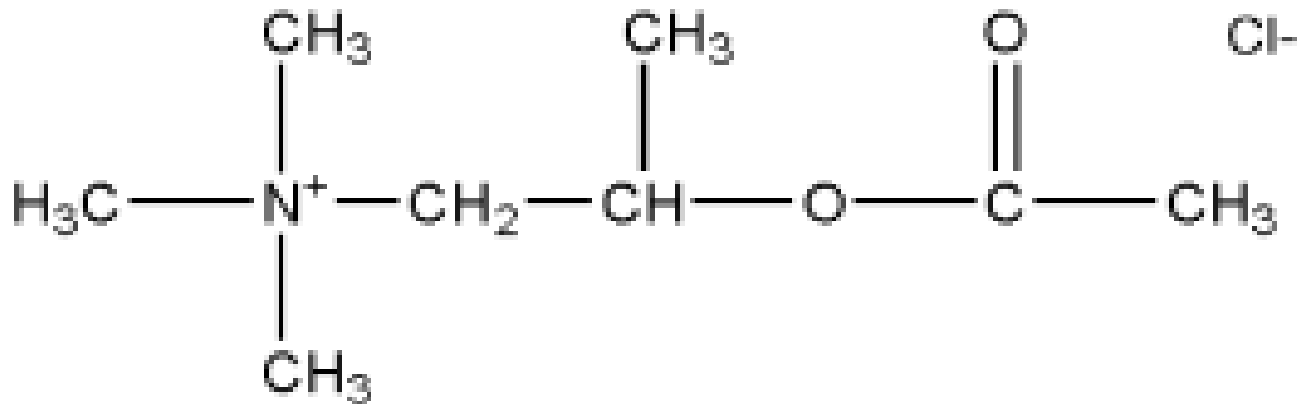
- *Acetylcholine Chloride:*



Acetylcholine Chloride

Methacholine Chloride

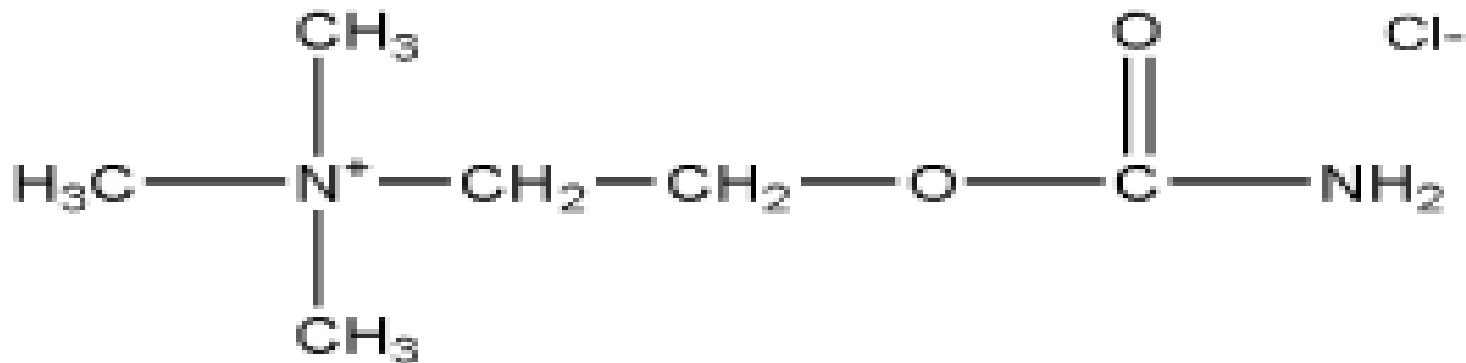
- Methacholine has sufficient stability in the body to give sustained parasympathetic stimulation.



Methacholine Chloride

Carbachol

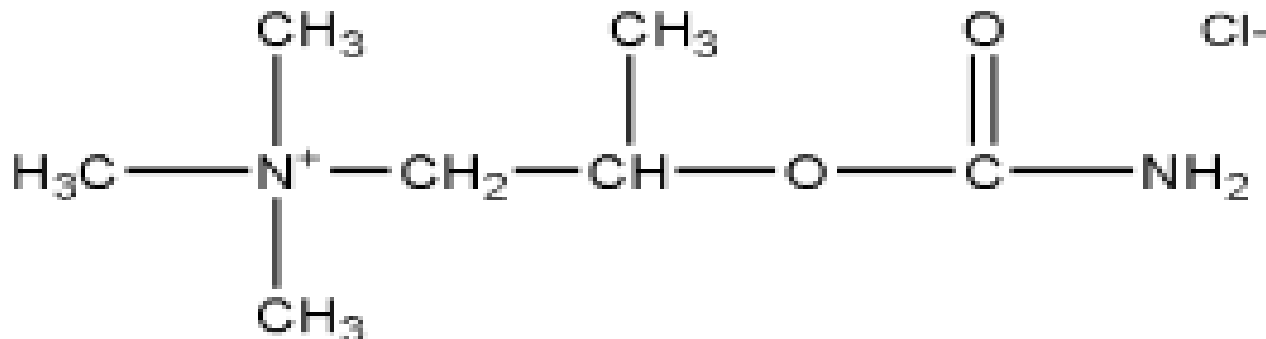
- Like ACh, carbachol is nonspecific in its action on muscarinic receptor subtypes.
- Has weak AChE inhibitory effect.
- it does not have cardiovascular activity.



Carbachol Chloride

Bethanechol Chloride

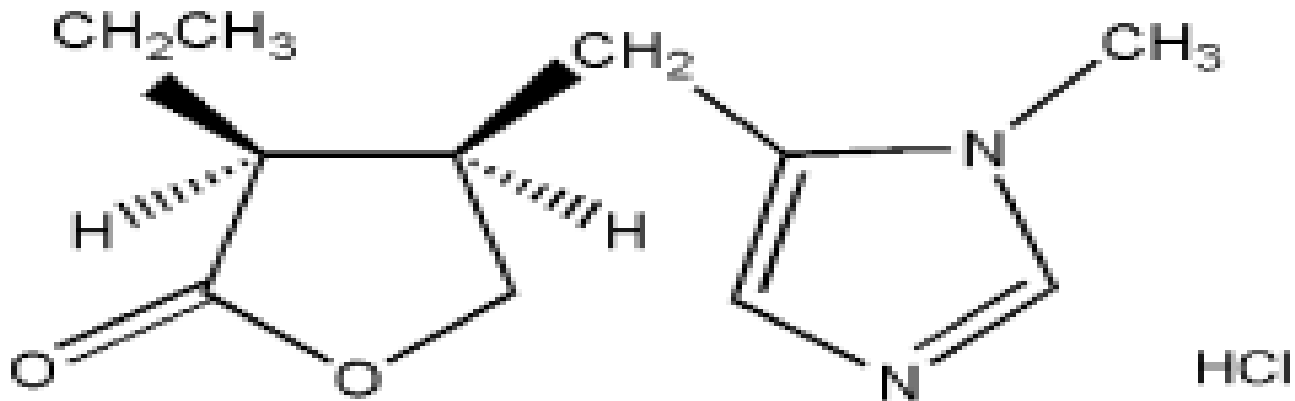
- Is nonspecific in its action on muscarinic receptor subtypes but appears to be more effective at eliciting pharmacological action of M3 receptors.



Bethanechol Chloride

Pilocarpine Hydrochloride

- Pilocarpine is a nonselective agonist on the muscarinic receptors.
- Used in the treatment of glaucoma.



Pilocarpine Hydrochloride

Cholinesterase Inhibitors

- These inhibitors are indirect-acting cholinergic agonists.
- There are two types of cholinesterases in humans, AChE and butyrylcholinesterase (BuChE). The cholinesterases differ in their location in the body and their substrate specificity.

AChE inhibitors

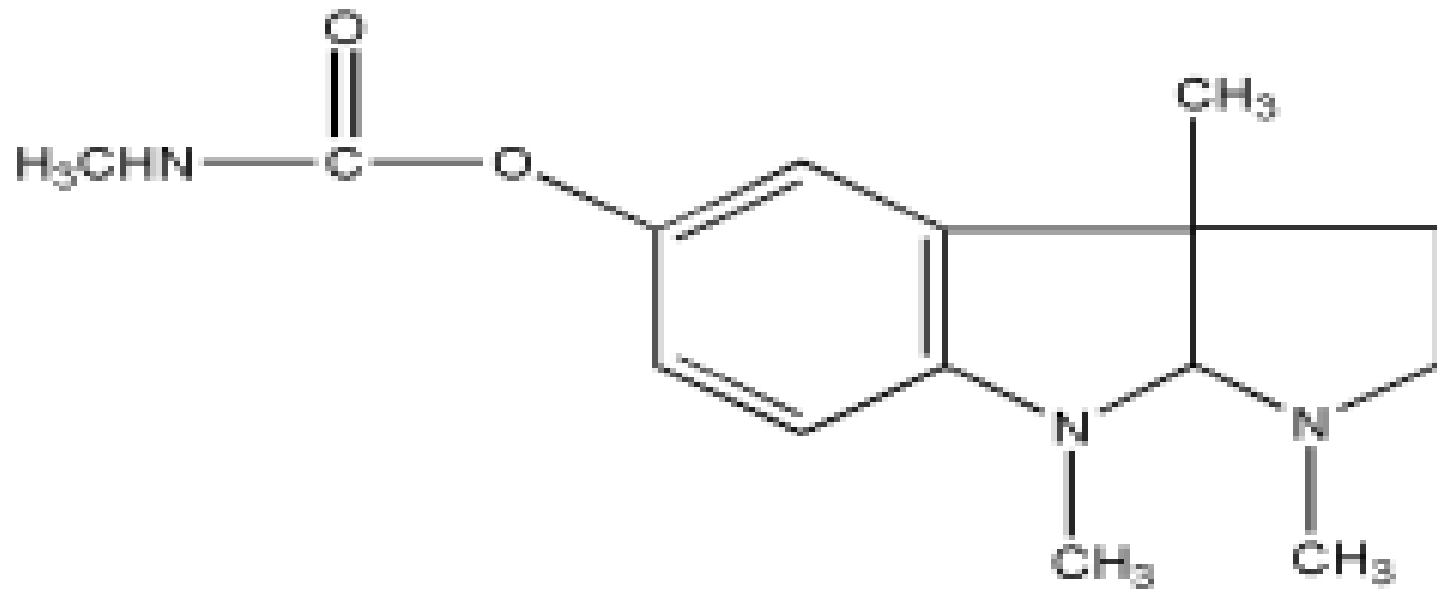
- have been used in the treatment of myasthenia gravis, atony in the GI tract, and glaucoma.
- They have also been used as agricultural insecticides and nerve gases.
- More recently, they have received attention as symptomatic drug treatments in patients suffering from Alzheimer disease.

BuChE (pseudocholinesterase)

- is located in human plasma.
- it has catalytic properties similar to those of AChE.
- The substrate specificity is broader, and it may hydrolyze dietary esters (like?) and drug molecules in the blood.

Reversible Inhibitors:

- Physostigmine, USP:



Physostigmine

Neostigmine Bromide

Pyridostigmine Bromide

Rivastigmine

Tacrine Hydrochloride

What are the differences?

Any question?

References:

- Wilson and Gisvold's Textbook of Organic Medicinal And Pharmaceutical Chemistry, 12th Edition.

Thank you